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<b>(54) Title:</b> NITROSATED AND NITROSYLATED COMPOUNDS AND COMPOSITIONS AND THEIR USE FOR TREATING RESPIRATORY DISORDERS		
<b>(57) Abstract</b>  Disclosed are (i) compounds of a steroid, a $\beta$ -agonist, an anticholinergic, a mast cell stabilizer and a phosphodiesterase (PDE) inhibitor directly or indirectly linked to a NO or NO <sub>2</sub> group or a group which stimulates endogenous production of NO or EDRF <i>in vivo</i> ; (ii) compositions of steroids, $\beta$ -agonists, anticholinergics, mast cell stabilizers and PDE inhibitors, which can optionally be substituted with at least one NO or NO <sub>2</sub> moiety or a group which stimulates endogenous production of NO or EDRF <i>in vivo</i> , and a compound that donates, transfers or releases nitric oxide as a charged species, i.e., nitrosonium (NO <sup>+</sup> ) or nitroxyl (NO <sup>-</sup> ), or as the neutral species, nitric oxide (NO) or that stimulates endogenous production of NO or EDRF <i>in vivo</i> ; and (iii) uses for them in preventing and/or treating respiratory disorders.		

**NITROSATED AND NITROSYLATED  
COMPOUNDS AND COMPOSITIONS AND THEIR  
USE FOR TREATING RESPIRATORY DISORDERS**

The present invention relates to the field of compounds, compositions and uses therefore, in oral and/or nasal administration prophylaxis and/or treatment of respiratory disorders. More particularly the invention relates to nitrosated and nitrosylated compounds, compositions comprising such compounds, which can optionally be unsubstituted or substituted with at least one NO or NO<sub>2</sub> moiety, and a compound that donates, transfers or releases nitric oxide as a charged species, *i.e.*, nitrosonium (NO<sup>+</sup>) or nitroxyl (NO<sup>-</sup>), or as the neutral species, nitric oxide (NO); and uses for each of them.

A broad spectrum of respiratory diseases and disorders have been recognized, many of which have overlapping and interacting etiologies. One of the most widespread and prevalent of these diseases in western populations is the chronic disease referred to as "asthma". Other such disorders are also characterized by acute pulmonary vasoconstriction such as may result from pneumonia, traumatic injury, aspiration or inhalation injury, fat embolism in the lung, acidosis inflammation of the lung, adult respiratory distress syndrome, acute pulmonary edema, acute mountain sickness, post-cardiac surgery, acute pulmonary hypertension, persistent pulmonary hypertension of the newborn, perinatal aspiration syndrome, hyaline membrane disease, acute pulmonary thromboembolism, heparin-protamine reactions, sepsis, status asthmaticus or hypoxia (including iatrogenic hypoxia) and other forms of reversible pulmonary vasoconstriction. Such pulmonary disorders also are also characterized by

Various categories of drugs are known to be useful in the inhalation of treatment of asthma. These include  $\beta_2$  agonists (such as salmeterol, albuterol, metaproterenol, terbutaline, pirbuterol, rimiterol, clenbuterol, bitolterol and repreterol, adrenalin, isoproterenol, ephedrine, orciprenlaine, fenoterol and isoetharine); anticholinergic agents (such as atropine, ipratropium, flutropium, tiotropium and rispenzepine) and mast cell stabilizers (chromolyn and nedocromil). Selective  $\beta$  agonists have recently been developed with fewer cardiotoxic side effects than those previously employed and are now considered suitable therapeutics for management of bronchitis and, particularly, emphysema, for which there previously had not been a suitable effective form of therapy.

Although corticosteroids are not generally indicated for routine use in the treatment of asthma, whether acute or chronic, they are used in large doses in the treatment of status asthmaticus. Nonetheless, the use of inhaled corticosteroids for the treatment of bronchial asthma has increased in recent years. Most frequently beclomethasone dipropionate, triamcinolone acetonide or flunisolide can be used to reduce or replace oral corticosteroid therapy, particularly in the treatment of children. This avoids or reduces bronchial reactivity and behavioral toxicity. See Cott and Cherniack, *Steroids and "Steroid-sparing Agents in Asthma"*, *New Engl. J. Med.*, 318:634-636, 1988.

Cystic fibrosis is a multi-organ disorder of the exocrine glands which is congenital, lethal and affects all populations, particularly European and North American populations. Primary effects of cystic fibrosis are in the secretory glands, particularly mucous secretion. One of the organ systems most effected by cystic fibrosis is the lungs and respiratory tract. Therapy is as yet only symptomatic as the underlying genetic defect has yet to be characterized.

The present invention is based on the discovery by the inventors that it is possible to directly or indirectly link an NO or NO<sub>2</sub> group or a group which stimulates the endogenous production of NO or endothelium-derived relaxing factor (EDRF) *in vivo*, to a steroid, a  $\beta$ -agonist, an anticholinergic, a mast cell stabilizer or a phosphodiesterase (PDE) inhibitor and that the resulting compound has beneficial therapeutic effects of both a steroid, a  $\beta$ -agonist, an anticholinergic, a mast cell stabilizer, or PDE inhibitor and an NO donor or stimulator.

In another aspect the invention provides a method for treating respiratory disorders, such as asthma, in an individual in need thereof which comprises administering to the individual a therapeutically effective amount of a steroid, a  $\beta$ -agonist, an anticholinergic, a mast cell stabilizer or a PDE inhibitor to which is directly or indirectly linked at least one NO or NO<sub>2</sub> group and/or a group that stimulates endogenous production of NO or EDRF *in vivo*.

In another aspect the invention provides a method of treating respiratory disorders, such as asthma, in an individual in need thereof which comprises administering to the individual (i) a therapeutically effective amount of a steroid, a  $\beta$ -agonist, an anticholinergic, a mast cell stabilizer or a PDE inhibitor, which optionally may be substituted with at least one NO or NO<sub>2</sub> group or a group that stimulates endogenous production of NO or EDRF *in vivo*, and (ii) a compound that donates, transfers or releases nitric oxide, and/or a group that stimulates production of NO or EDRF *in vivo*.

The steroid,  $\beta$ -agonist, anticholinergic, mast cell stabilizer or PDE inhibitor and the compound that donates, transfers or releases nitric oxide and/or stimulates endogenous production of NO or EDRF *in vivo* can be administered separately or as components of the same composition in one or more pharmaceutically acceptable carriers.

The following drawings are illustrative of embodiments of the invention and do not limit the scope of the invention as defined by the claims.

Figure 1 illustrates a synthetic pathway for the preparation of nitrite containing steroid derivatives.

Figure 2 illustrates a synthetic pathway for the preparation of nitrosothiol containing steroid derivatives.

Figure 3 illustrates a synthetic pathway for the preparation of nitrate containing steroid derivatives.

Figure 15 illustrates a synthetic pathway for the preparation of nitrate containing rispenzepine derivatives.

Figure 16 illustrates a synthetic pathway for the preparation of 2-hydroxy-2-nitrosohydrazine containing rispenzepine derivatives.

Figure 17 illustrates a synthetic pathway for the preparation of nitrite containing rispenzepine derivatives.

Figure 18 illustrates a synthetic pathway for the preparation of nitrosothiol containing rispenzepine derivatives.

Figure 19 illustrates a synthetic pathway for the preparation of nitrate containing rispenzepine derivatives.

Figure 20 illustrates a synthetic pathway for the preparation of 2-hydroxy-2-nitrosohydrazine containing rispenzepine derivatives.

Figure 21 illustrates a synthetic pathway for the preparation of nitrite containing mast cell stablizer derivatives.

Figure 22 illustrates a synthetic pathway for the preparation of nitrosothiol containing mast cell stablizer derivatives.

Figure 23 illustrates a synthetic pathway for the preparation of nitrate containing mast cell stablizer derivatives.

Figure 24 illustrates a synthetic pathway for the preparation of 2-hydroxy-2-nitrosohydrazine containing mast cell stablizer derivatives.

Figure 25 illustrates a synthetic pathway for the preparation of sidnonimine containing mast cell stablizer derivatives.

The term "alkenyl" as used herein refers to a branched or straight chain  $C_2$ - $C_{10}$  hydrocarbon which also comprises one or more carbon-carbon double bonds.

The term "amino" as used herein refers to  $-NH_2$ .

The term "carboxy" as used herein refers to  $-C(O)O-$ .

The term "nitrate" as used herein refers to  $-O-NO_2$ .

The term "nitrite" as used herein refers to  $-O-NO$ .

The term "alkylamino" as used herein refers to  $R_{51}NH$ -wherein  $R_{51}$  is a lower alkyl group as defined above, for example, methylamino, ethylamino, butylamino, and the like.

The term "dialkylamino" as used herein refers to  $R_{52}R_{53}N$ -wherein  $R_{52}$  and  $R_{53}$  are independently selected from lower alkyl groups as defined above, for example dimethylamino, diethylamino, methyl propylamino and the like.

The term "nitro" as used herein refers to the group  $-NO_2$  and "nitrosated" refers to compounds that have been substituted therewith.

The term "nitroso" as used herein refers to the group  $-NO$  and "nitrosylated" refers to compounds that have been substituted therewith.

The term "aryl" as used herein refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl, and the like. Aryl groups (including bicyclic aryl groups) can be unsubstituted or substituted with one, two or three substituents independently selected from loweralkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, and nitro. In addition, substituted aryl groups include tetrafluorophenyl and pentafluorophenyl.

The term "halogen" or "halo" as used herein refers to I, Br, Cl, or F. The term "haloalkyl" as used herein refers to a lower alkyl radical, as defined above, bearing at least one halogen substituent, for example, chloromethyl, fluoroethyl or trifluoromethyl and the like.

The term "haloalkyl" as used herein refers to a lower alkyl radical to which is appended one or more halogens. Representative examples of a haloalkyl group include trifluoromethyl, chloromethyl, 2-bromobutyl, 1-bromo-2-chloro-pentyl and the like.

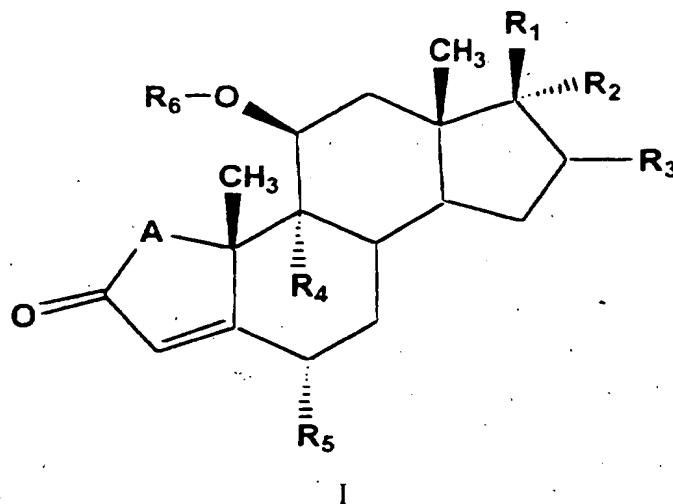
The term "haloalkoxy" as used herein refers to a haloalkyl radical to which is appended an alkoxy group. Representative examples of haloalkoxy groups include fluoromethoxy, 1,1,1-trichloroethoxy, 2-bromobutoxy and the like.

The term "halide" refers to the monovalent anions chloride, bromide, and iodide.

The term "heteroaryl" as used herein refers to a mono- or bi-cyclic ring system containing one or two aromatic rings and containing at least one nitrogen, oxygen, or sulfur atom in an aromatic ring. Heteroaryl groups (including bicyclic heteroaryl groups) can be unsubstituted or substituted with one, two or three substituents independently selected from lower alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, hydroxy, halo and nitro. Examples of heteroaryl groups include but are not limited to pyridine, pyrazine, pyrimidine, pyridazine, pyrazole, triazole, thiazole, isothiazole, benzothiazole, benzoxazole, thiadiazole, oxazole, pyrrole, imidazole and isoxazole.

The term "heterocyclic ring" refers to any 3-, 4-, 5-, 6-, or 7-membered nonaromatic ring containing at least one nitrogen atom, oxygen, or sulfur.

The term "arylheterocyclic ring" as used herein refers to a bi- or tricyclic ring comprised of an aryl ring as previously defined appended via two adjacent carbons of the aryl group to a heterocyclic ring as previously defined.



wherein

A is selected from  $-\text{CH}=\text{CH}-$  or  $-\text{CH}_2-\text{CH}_2-$ ;

$\text{R}_1$  is selected from

(1)  $-\text{C}(\text{O})\text{CH}_2-\text{B}-\text{D}$  wherein B is oxygen or sulfur; D is selected from (i)  $-\text{NO}$ ; (ii)  $-\text{NO}_2$ ; (iii)  $-\text{C}(\text{R}_d)-\text{O}-\text{C}(\text{O})-\text{Y}-[\text{C}(\text{R}_e)(\text{R}_f)]_p-\text{T}-\text{Q}$  in which  $\text{R}_d$  is hydrogen, lower alkyl, cycloalkyl, aryl, alkylaryl, aryl or heteroaryl, Y is oxygen, sulfur, or  $\text{NR}_i$  in which  $\text{R}_i$  is hydrogen, lower alkyl, lower haloalkyl, or heteroaryl,  $\text{R}_e$  and  $\text{R}_f$  are at each occurrence independently selected from hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, alkyl, heteroaryl, arylalkyl, alkylamino, dialkylamino, carboxy, carboxamido, or taken together are carbonyl, cycloalkyl or bridged cycloalkyl, p is an integer from 1 to 6, T is a covalent bond, oxygen, sulfur or nitrogen and Q is selected from  $-\text{NO}$  or  $-\text{NO}_2$ ; (iv)  $-\text{C}(\text{O})-\text{T}^1-[\text{C}(\text{R}_e)(\text{R}_f)]_p-\text{T}^2-\text{Q}$  wherein  $\text{T}^1$  and  $\text{T}^2$  are independently selected from T and  $\text{R}_e$ ,  $\text{R}_f$ , p, Q, and T are as defined above; (v)  $-\text{C}(\text{O})-\text{T}[\text{C}(\text{R}_y)(\text{R}_z)]_p$  wherein  $\text{R}_y$  and  $\text{R}_z$  are independently selected from  $-\text{T}^1-[\text{C}(\text{R}_e)(\text{R}_f)]_p-\text{G}-[\text{C}(\text{R}_e)(\text{R}_f)]_p-\text{T}^2-\text{Q}$  wherein G is (i) a covalent bond; (ii)  $-\text{T}-\text{C}(\text{O})-$ ; (iii)  $-\text{C}(\text{O})-\text{T}$ , or (iv) Y, and wherein  $\text{R}_d$ ,  $\text{R}_e$ ,  $\text{R}_f$ , p, Q, T, and Y are as defined above;

(2)  $-\text{C}(\text{O})-\text{C}(\text{O})-\text{O}-\text{R}_i$  wherein  $\text{R}_i$  is as defined above;

(3)  $-\text{C}(\text{O})-\text{B}-\text{R}_i$  wherein B and  $\text{R}_i$  are as defined above;

(4)  $-\text{C}(\text{O})-\text{CH}_2-\text{B}-\text{C}(\text{O})-\text{R}_i$  wherein B and  $\text{R}_i$  are as defined above;

(5)  $-\text{C}(\text{O})-\text{CH}_2-\text{X}$  wherein X is halogen;

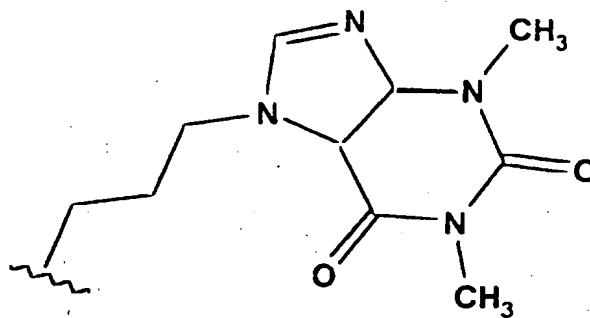
(6)  $-\text{S}-\text{R}_i$  wherein  $\text{R}_i$  is as defined above;

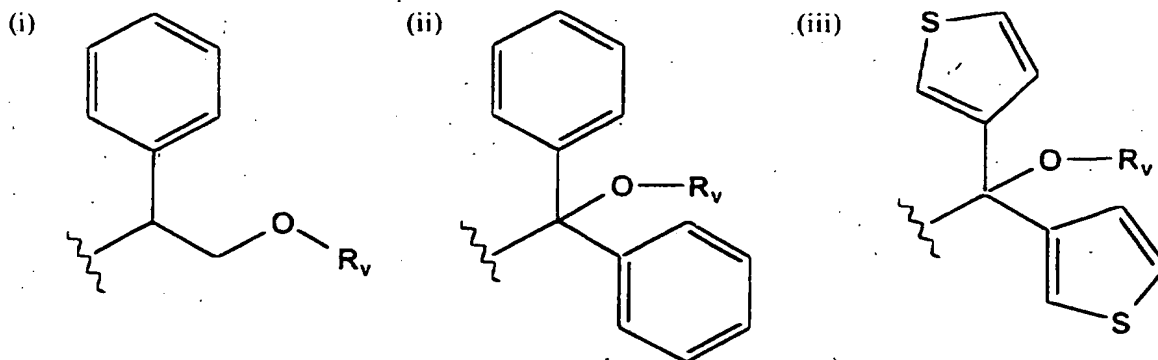


(i) lower alkyl

(ii)  $-(\text{CH}_2)_p-\text{O}-(\text{CH}_2)_a-\text{C}_6\text{H}_5$  wherein a is an integer from 1 to 4 and p is as defined above;

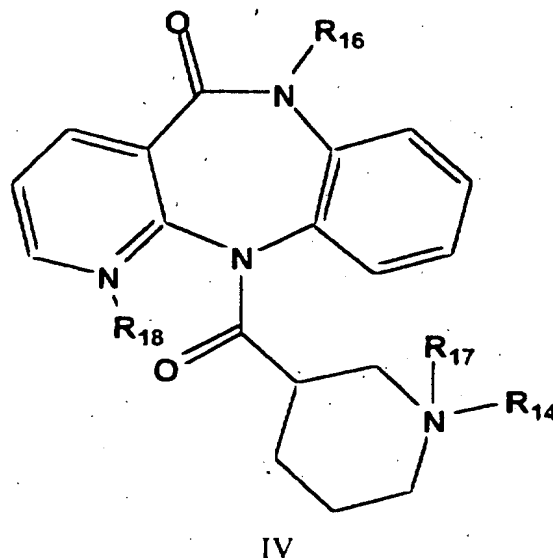
(iii)





wherein  $R_v$  is selected from D or M and D and M are as defined above;

Another embodiment of this aspect provides compounds having the structure:



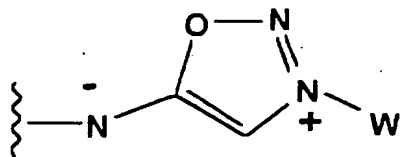
wherein

$R_{14}$  is as defined above;

$R_{16}$  is selected from hydrogen,  $-C(R_d)-O-C(O)-Y-[C(R_e)(R_f)]_p-T-Q$ ,  $-C(O)-T^1-[C(R_e)(R_f)]_p-T^2-Q$ , or M; and wherein  $R_d$ ,  $R_e$ ,  $R_f$ , M, p, T,  $T^1$ ,  $T^2$ , Q, and Y are defined as above; and

$R_{17}$  and  $R_{18}$  are independently selected from a lone pair of electrons,  $-C(R_d)-O-C(O)-Y-[C(R_e)(R_f)]_p-T-Q$ , or M wherein  $R_d$ ,  $R_e$ ,  $R_f$ , M, p, T, Q, and Y are defined as above with the provision that  $R_{17}$  and/or  $R_{18}$  must be  $-C(R_d)-O-C(O)-Y-[C(R_e)(R_f)]_p-T-Q$  or M when  $R_{16}$  is hydrogen;

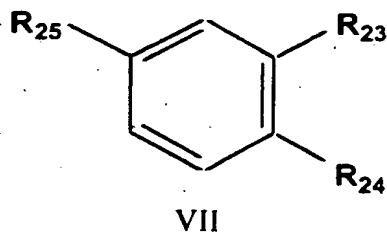
$R_d$ ,  $R_e$ ,  $R_f$ ,  $p$ ,  $Q$  and  $T$  are as defined above; (2)  $T-[C(R_e)(R_f)]_p-H-[C(R_e)(R_f)]_p-N[N-(O-)N=O]-R_i$  wherein  $R_d$ ,  $R_e$ ,  $R_f$ ,  $R_i$ ,  $p$ ,  $H$  and  $T$  are as defined above; (3)



in which  $W$  is a heterocyclic ring or  $NR_sR'_s$ , wherein  $R_s$  and  $R'_s$  are independently selected from lower alkyl, aryl or alkenyl; (4) sodium or (5) hydrogen;

$R_{22}$  is hydrogen,  $M$ , or  $D$  with the provision that  $R_{22}$  must be  $M$  or  $D$  when  $R_{20}$  and  $R_{21}$  are selected as sodium or hydrogen;

Another embodiment of this aspect provides compounds having the structure:



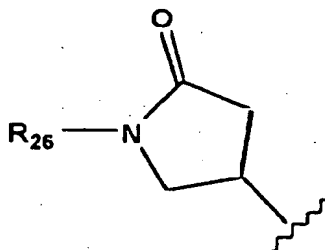
wherein,

$R_{23}$  is alkoxy, cycloalkoxy, or halogen;

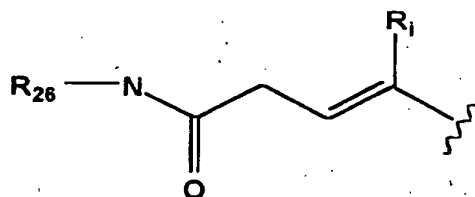
$R_{24}$  is hydrogen, alkoxy, or haloalkoxy; and

$R_{25}$  is selected from:

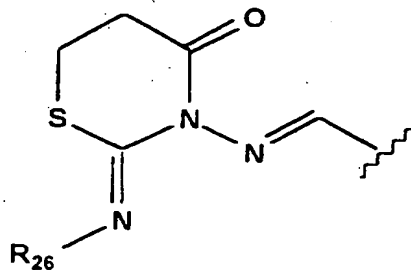
(i)



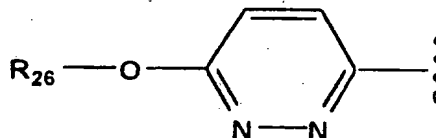
(ii)



(iii)



(iv)



undesirable reactions during a synthetic procedure and many such protecting groups are known, *c.f.*, T.H. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York (1991).

One embodiment of this aspect provides processes for making compounds having structures I and to the intermediates useful in such processes as follows.

Nitroso compounds of formula (I) wherein A, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>e</sub>, R<sub>f</sub>, and p are defined as above and an O-nitrosylated ester is representative of the R<sub>1</sub> group as defined above may be prepared as outlined in Figure 1. The alcohol group of formula 1 is converted to the ester of formula 2 wherein p, R<sub>e</sub> and R<sub>f</sub> are defined as above by reaction with an appropriate protected alcohol containing activated acylating agent wherein P<sup>1</sup> is as defined above. Preferred methods for the formation of esters are reacting the alcohol with the preformed acid chloride or symmetrical anhydride of the protected alcohol containing acid or condensing the alcohol and protected alcohol containing acid in the presence of a dehydrating agent such as dicyclohexylcarbodiimide (DCC) or 1-ethyl-3(3-dimethylaminopropyl)carbodiimide hydrochloride (EDAC · HCl) with or without a catalyst such as dimethylaminopyridine (DMAP) or 1-hydroxybenzotriazole (HOBt). Preferred protecting groups for the alcohol moiety are silyl ethers such as a trimethylsilyl or a tert-butyldimethylsilyl ether. Deprotection of the hydroxyl moiety (fluoride ion is the preferred method for removing silyl ether protecting groups) followed by reaction a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl dinitrite, or nitrosonium tetrafluoroborate in a suitable anhydrous solvent such as dichloromethane, THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethylamine affords the compound of the formula IA.

Nitroso compounds of formula (I) wherein A, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>e</sub>, R<sub>f</sub>, and p are defined as above and an S-nitrosylated ester is representative of the R<sub>1</sub> group as defined above may be prepared as outlined in Figure 2. The alcohol group of the formula 1 is converted to the ester of the formula 3 wherein p, R<sub>e</sub> and R<sub>f</sub> are defined as above by reaction with an appropriate protected thiol containing activated acylating agent wherein P<sup>2</sup> is as defined above. Preferred methods for the formation of esters are reacting the alcohol with the preformed acid chloride or symmetrical anhydride of the protected thiol containing acid or condensing the alcohol and protected thiol containing acid in the presence of a dehydrating agent

wherein  $P^3$  is as defined above. Preferred methods for the formation of esters are reacting the alcohol with the preformed acid chloride or symmetrical anhydride of the protected amino containing acid or condensing the alcohol and protected amine containing acid in the presence of a dehydrating agent such as DCC or EDAC. HCl with or without a catalyst such as DMAP or HOBt. Preferred protecting groups for the amine are as a carbamate such as a t-butyl carbamate or a 9-fluorenylmethyl carbamate or an amide such as a trifluoroacetamide. Deprotection of the amino moiety (strong acid such as HCl in dioxane or trifluoroacetic acid is used to remove a t-butyl carbamate while piperidine is used to remove 9-fluorenylmethyl carbamate while mild aqueous or alcoholic base may be used to cleave a trifluoroacetamide group) followed by treatment of the amine with nitric oxide (1-5 atmospheres) in a dry inert solvent such as ether or tetrahydrofuran affords the compound of the formula **ID**.

Another embodiment of this aspect provides processes for making compounds having structures **II** and to the intermediates useful in such processes as follows.

Nitroso compounds of formula **(II)** wherein E,  $R_9$ ,  $R_{10}$ ,  $R_e$ ,  $R_f$ , and p are defined as above, Z and  $R_{11}$  are hydrogen, and an O-nitrosylated ester is representative of the  $R_8$  group as defined above may be prepared as outlined in Figure 5. The amine,  $1^\circ$ , and  $2^\circ$  alcohol groups of formula 5 are protected to afford the compound of the formula 6. Preferred protecting groups for the amine are as a carbamate such as a benzyl carbamate or an amide such as a trifluoroacetamide while preferred protecting groups for  $1^\circ$  and  $2^\circ$  alcohol moieties are as benzyl ethers. The phenolic group(s) of formula 6 is converted to the ester(s) of formula 7 wherein p,  $R_e$  and  $R_f$  are defined as above by reaction with an appropriate protected alcohol containing activated acylating agent wherein  $P^1$  is as defined above. Preferred methods for the formation of esters are reacting the alcohol with the preformed acid chloride or symmetrical anhydride of the protected alcohol containing acid or condensing the alcohol and protected alcohol containing acid in the presence of a dehydrating agent such as DCC or EDAC. HCl with or without a catalyst such as DMAP or HOBt. Preferred protecting groups for the alcohol moiety are silyl ethers such as a trimethylsilyl or tert-butyldimethylsilyl ether. Deprotection of the hydroxyl moieties (fluoride ion is the preferred method for removing silyl ether protecting groups) followed by reaction a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl dinitrite, or nitrosonium tetrafluoroborate in a suitable anhydrous solvent such as dichloromethane, THF, DMF, or acetonitrile with or without an amine base such as pyridine or

of a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl dinitrite, a lower alkyl nitrite such as tert-butyl nitrite, or nitrosonium tetrafluoroborate in a suitable anhydrous solvent such as methylene chloride, THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethylamine affords the compound of the formula **IIB**. Alternatively, treatment of compound **11** with a stoichiometric quantity of sodium nitrite in an acidic aqueous or alcoholic solution affords the compound of the formula **IIB**.

Nitro compounds of formula (**II**) wherein E, R<sub>9</sub>, R<sub>10</sub>, R<sub>c</sub>, R<sub>f</sub>, and p are defined as above, Z and R<sub>11</sub> are hydrogen, and a O-nitrosated ester is representative of the R<sub>8</sub> group as defined above may be prepared as outlined in Figure 7. The amine, 1<sup>0</sup>, and 2<sup>0</sup> alcohol groups of formula **5** are protected to afford the compound of the formula **12**. Preferred protecting groups for the amine are as a carbamate such as a t-butyl carbamate or an amide such as a trifluoroacetamide while preferred protecting groups for 1<sup>0</sup> and 2<sup>0</sup> alcohol moieties are as silyl ethers such as trimethylsilyl or t-butyldimethylsilyl ethers. The phenolic group(s) of the formula **12** is converted to the ester(s) of the formula **13** wherein p, R<sub>c</sub> and R<sub>f</sub> are defined as above by reaction with an appropriate nitrate containing activated acylating agent. Preferred methods for the formation of esters are reacting the alcohol with the preformed acid chloride or symmetrical anhydride of the protected thiol containing acid or condensing the alcohol and protected thiol containing acid in the presence of a dehydrating agent such as DCC or EDAC HCl with or without a catalyst such as DMAP or HOBt. Deprotection of the amine (strong acid such as HCl in dioxane or trifluoroacetic acid is used to remove a t-butyl carbamate) and hydroxyl moieties (fluoride ion is the preferred method for removing silyl ether protecting groups) affords a compound of the formula **IIC**.

2-Hydroxy-2-nitrosohydrazine compounds of formula (**II**) wherein E, Z, R<sub>9</sub>, R<sub>10</sub>, R<sub>c</sub>, R<sub>f</sub>, R<sub>i</sub>, and p are defined as above and a 2-hydroxy-2-nitrosohydrazine ester is representative of the R<sub>8</sub> group as defined above may be prepared as outlined in Figure 8. The amine, 1<sup>0</sup>, and 2<sup>0</sup> alcohol groups of formula **5** are protected to afford the compound of the formula **12**. Preferred protecting groups for the amine are as a carbamate such as a t-butyl carbamate or an amide such as a trifluoroacetamide while preferred protecting groups for 1<sup>0</sup> and 2<sup>0</sup> alcohol moieties are as silyl ethers such as trimethylsilyl or t-butyldimethylsilyl ethers. The phenolic group(s) of the formula **12** is converted to the ester of the formula **14**

Nitroso compounds of formula (III) wherein aryl, heteroaryl,  $R_{12}$ ,  $R_{13}$ ,  $R_{14}$ ,  $R_e$ ,  $R_f$ , and  $p$  are defined as above and an S-nitrosylated ester is representative of the  $R_{15}$  group as defined above may be prepared as outlined in Figure 10. The alcohol group of the formula 15 is converted to the ester of the formula 17 wherein  $p$ ,  $R_e$  and  $R_f$  are defined as above by reaction with an appropriate protected thiol containing activated acylating agent wherein  $P^2$  is as defined above. Preferred methods for the formation of esters are reacting the alcohol with the preformed acid chloride or symmetrical anhydride of the protected thiol containing acid or condensing the alcohol and protected thiol containing acid in the presence of a dehydrating agent such as DCC or EDAC·HCl with or without a catalyst such as DMAP or HOBt. Preferred protecting groups for the thiol moiety are as a thioester such as a thioacetate or thiobenzoate, as a disulfide, as a thiocarbamate such as N-methoxymethyl thiocarbamate, or as a thioether such as a paramethoxybenzyl thioether, a tetrahydropyranyl thioether or a 2,4,6-trimethoxybenzyl thioether. Deprotection of the thiol moiety (zinc in dilute aqueous acid, triphenylphosphine in water and sodium borohydride are preferred methods for reducing disulfide groups while aqueous base is typically utilized to hydrolyze thioesters and N-methoxymethyl thiocarbamates and mercuric trifluoroacetate, silver nitrate, or strong acids such as trifluoroacetic or hydrochloric acid and heat are used to remove a paramethoxybenzyl thioether, a tetrahydropyranyl thioether, or a 2,4,6-trimethoxybenzyl thioether group) followed by reaction a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl dinitrite, a lower alkyl nitrite such as tert-butyl nitrite, or nitrosonium tetrafluoroborate in a suitable anhydrous solvent such as methylene chloride, THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethylamine affords the compound of the formula IIIB. Alternatively, treatment of compound 17 with a stoichiometric quantity of sodium nitrite in an acidic aqueous or alcoholic solution affords the compound of the formula IIIB.

Nitro compounds defined ester of formula (III) wherein aryl, heteroaryl,  $R_{12}$ ,  $R_{13}$ ,  $R_{14}$ ,  $R_e$ ,  $R_f$ , and  $p$  are defined as above and an O-nitrosated ester is representative of the  $R_{15}$  group as defined above may be prepared as outlined in Figure 11. The alcohol group of the formula 15 is converted to the ester of the formula IIIC wherein  $p$ ,  $R_e$  and  $R_f$  are defined as above by reaction with an appropriate nitrate containing activated acylating agent. Preferred methods for the formation of esters are reacting the alcohol with the preformed acid chloride or

alcohol and protected thiol containing acid in the presence of a dehydrating agent such as DCC or EDAC . HCl with a catalyst such as DMAP. Preferred protecting groups for the alcohol moiety are silyl ethers such as a tert-butyldimethylsilyl ether. Deprotection of the hydroxyl moiety (fluoride ion is the preferred method for removing silyl ether protecting groups) followed by reaction a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl dinitrite, or nitrosonium tetrafluoroborate in a suitable anhydrous solvent such as dichloromethane, THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethylamine affords the compound of the formula **IVA**.

Nitroso compounds of formula (IV) wherein  $R_{14}$ ,  $R_{17}$ ,  $R_{18}$ ,  $R_e$ ,  $R_f$ , and  $p$  are defined as above and an S-nitrosylated imide is representative of the  $R_{16}$  group as defined above may be prepared as outlined in Figure 14. The amide nitrogen of formula **19** is converted to the imide of the formula **21** wherein  $p$ ,  $R_e$  and  $R_f$  are defined as above by reaction with an appropriate protected thiol containing activated acylating agent wherein  $P^2$  is as defined above. Preferred methods for the formation of imides are reacting the alcohol with the preformed acid chloride or symmetrical anhydride of the protected thiol containing acid or condensing the alcohol and protected thiol containing acid in the presence of a dehydrating agent such as DCC or EDAC . HCl with a catalyst such as DMAP. Preferred protecting groups for the thiol moiety are as a thioester such as a thioacetate or thiobenzoate, as a disulfide, or as a thioether such as a paramethoxybenzyl thioether, a tetrahydropyranyl thioether or a 2,4,6-trimethoxybenzyl thioether. Deprotection of the thiol moiety (zinc in dilute aqueous acid, triphenylphosphine in water and sodium borohydride are preferred methods for reducing disulfide groups while mercuric trifluoroacetate, silver nitrate, or strong acids such as trifluoroacetic or hydrochloric acid and heat are used to remove a paramethoxybenzyl thioether, a tetrahydropyranyl thioether, or a 2,4,6-trimethoxybenzyl thioether group) followed by reaction a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl dinitrite, a lower alkyl nitrite such as tert-butyl nitrite, or nitrosonium tetrafluoroborate in a suitable anhydrous solvent such as methylene chloride, THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethylamine affords the compound of the formula **IVB**. Alternatively, treatment of compound **21** with a stoichiometric quantity of sodium nitrite in an acidic aqueous or alcoholic solution affords the compound of the formula **IVB**.



thiation reagent such as 2,4-bis(4-methoxyphenyl)-2,4-dithioxo-1,2,3,4-dithiadiphosphetane or phosphorus pentasulfide. Alkylation of compound of the formula 23 with an appropriate protected alcohol containing alkylating agent affords a compound of the formula 24 wherein p, R<sub>e</sub>, R<sub>f</sub>, and P<sup>1</sup> are defined as above. Preferred alkylating agents are alkyl halides or sulfonates while preferred protecting groups for the alcohol moiety are silyl ethers such as a trimethylsilyl or a tert-butyldimethylsilyl ether. Deprotection of the hydroxyl moiety (fluoride ion is the preferred method for removing silyl ether protecting groups) followed by reaction a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl dinitrite, or nitrosonium tetrafluoroborate in a suitable anhydrous solvent such as dichloromethane, THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethylamine affords the compound of the formula VA.

Nitroso compounds of formula (V) wherein R<sub>14</sub>, R<sub>17</sub>, R<sub>18</sub>, R<sub>e</sub>, R<sub>f</sub>, and p are defined as above and an S-nitrosylated isothioamide is representative of the R<sub>19</sub> group as defined above may be prepared as outlined in Figure 18. Alkylation of compound of the formula 23 with an appropriate protected thiol containing alkylating agent affords a compound of the formula 25 wherein p, R<sub>e</sub>, R<sub>f</sub>, and P<sup>2</sup> are defined as above. Preferred alkylating agents are alkyl halides or sulfonates while preferred protecting groups for the thiol moiety are as a thioester such as a thioacetate or thiobenzoate, as a disulfide, or as a thioether such as a 2,4,6-trimethoxybenzyl thioether. Deprotection of the thiol moiety (zinc in dilute aqueous acid, triphenylphosphine in water and sodium borohydride are preferred methods for reducing disulfide groups, mild aqueous or alcoholic base is used to cleave thioesters strong acids such as trifluoroacetic or hydrochloric acid are used to remove a 2,4,6-trimethoxybenzyl thioether group) followed by reaction with a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl dinitrite, a lower alkyl nitrite such as tert-butyl nitrite, or nitrosonium tetrafluoroborate in a suitable anhydrous solvent such as methylene chloride, THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethylamine affords the compound of the formula VB. Alternatively, treatment of compound 25 with a stoichiometric quantity of sodium nitrite in an acidic aqueous or alcoholic solution affords the compound of the formula VB.

Nitro compounds of formula (V) wherein R<sub>14</sub>, R<sub>17</sub>, R<sub>18</sub>, R<sub>e</sub>, R<sub>f</sub>, and p are defined as above and an O-nitrosated isothioamide is representative of the R<sub>19</sub>

alcohol and protected alcohol containing acid in the presence of a dehydrating agent such as DCC or EDAC · HCl with or without a catalyst such as DMAP or HOBt. Preferred protecting groups for the alcohol moiety are silyl ethers such as a tert-butyldimethylsilyl ether. Deprotection of the acid and hydroxyl moieties (strong acid such as HCl in dioxane or trifluoroacetic acid cleaves t-butyl esters while fluoride ion is the preferred method for removing silyl ether protecting groups) followed by reaction a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl dinitrite, or nitrosonium tetrafluoroborate in a suitable anhydrous solvent such as dichloromethane, THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethylamine affords the compound of the formula VIA.

Nitroso compounds of formula (VI) wherein F,  $R_{21}$ ,  $R_{22}$ ,  $R_e$ ,  $R_f$ , and p are defined as above and an S-nitrosylated ester is representative of the  $R_{23}$  group as defined above may be prepared as outlined in Figure 22. The compound of the formula 30 is converted to the compound of the formula 31 by reaction of the alcohol group with an appropriate protected thiol containing activated acylating agent wherein  $R_e$ ,  $R_f$ , and p and  $P^2$  is as defined above. Preferred methods for the formation of esters are reacting the alcohol with the preformed acid chloride or symmetrical anhydride of the protected thiol containing acid or condensing the alcohol and protected thiol containing acid in the presence of a dehydrating agent such as DCC or EDAC · HCl with or without a catalyst such as DMAP or HOBt. Preferred protecting groups for the thiol moiety are as a thioester such as a thioacetate or thiobenzoate, as a disulfide, as a thiocarbamate such as N-methoxymethyl thiocarbamate, or as a thioether such as a paramethoxybenzyl thioether, a tetrahydropyranyl thioether or a 2,4,6-trimethoxybenzyl thioether. Deprotection of the thiol and acid moieties (zinc in dilute aqueous acid, triphenylphosphine in water and sodium borohydride are preferred methods for reducing disulfide groups while aqueous base is typically utilized to hydrolyze thioesters and N-methoxymethyl thiocarbamates and mercuric trifluoroacetate, silver nitrate, or strong acids such as trifluoroacetic or hydrochloric acid and heat are used to remove a paramethoxybenzyl thioether, a tetrahydropyranyl thioether, or a 2,4,6-trimethoxybenzyl thioether group as well as t-butyl esters) followed by reaction a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl dinitrite, a lower alkyl nitrite such as tert-butyl nitrite, or nitrosonium tetrafluoroborate in a suitable anhydrous solvent such as methylene chloride, THF, DMF, or acetonitrile with or without an amine base such as pyridine or

with nitric oxide (1-5 atmospheres) in a dry inert solvent such as ether or tetrahydrofuran affords the compound of the formula **VID**.

Sidnonimine compounds of formula (VI) wherein F, R<sub>22</sub>, R<sub>e</sub>, R<sub>f</sub>, and p are defined and a 6-W-substituted sydnonimine wherein W is as defined above is representative of the R<sub>20</sub> and R<sub>21</sub> groups as defined above may be prepared as outlined in Figure 25. The alcohol of formula 27 is protected to afford the compound of the formula 34. Preferred protecting groups for the alcohol are as a carbamate such as a t-butyl carbonate or a silyl ether such as a trimethylsilyl ether. The diacid of the formula 34 is converted into the dicarboximide of the formula 35 by reaction with a 6-W-substituted sydnonimine. Preferred methods for the preparation of carboximides are initially forming the dimixed anhydride via reaction of 34 with a chloroformate such as isobutylchloroformate in the presence of a non nucleophilic base such as triethylamine in an anhydrous inert solvent such as diethylether or THF. The dimixed anhydride is then reacted with the 6-W-substituted sydnonimine to afford 35. Alternatively, the diacid 34 and may be coupled to the 6-W-substituted sydnonimine afford 35 by treatment with a dehydration agent such as DCC or EDAC with or without a catalyst such as DMAP or HOBT. Alternatively, the diacid 34 may be converted into an active ester by reaction with a suitably substituted phenol utilizing any of the conditions for ester formation described, followed by reaction with the a 6-W-substituted sydnonimine. Preferred 6-W-substituted sydnonimines are 1,2,6,4-oxatriazolium, 6-amino-6-morpholine and are 1,2,6,4- oxatriazolium, 6-amino-6-(6-chloro-2-methyl -benzene) and preferred active esters are para-nitrophenyl, 2,4,6-trichlorophenyl, and pentafluorophenyl. Deprotection of the hydroxyl moiety (strong acid such as HCl or trifluoroacetic acid is used to cleave t-butyl carbonates while fluoride is the preferred method for removing silyl ethers) in the compound of the formula 35 affords the compound of the formula **VIE**.

Another embodiment of this aspect provides processes for making compounds having structures **VII** and to the intermediates useful in such processes as follows.

Nitroso compounds of formula (VII) wherein R<sub>23</sub>, R<sub>24</sub>, R<sub>e</sub>, R<sub>f</sub>, and p are defined as above and an O-nitrosylated imide is representative of the R<sub>25</sub> group as defined above may be prepared as outlined in Figure 26. The amide nitrogen of formula 36 is converted to the imide of formula 37 wherein p, R<sub>e</sub> and R<sub>f</sub> are

such as methylene chloride, THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethylamine affords the compound of the formula **VIIB**. Alternatively, treatment of compound **38** with a stoichiometric quantity of sodium nitrite in an acidic aqueous or alcoholic solution affords the compound of the formula **VIIB**.

Nitro compounds of formula (**VII**) wherein  $R_{23}$ ,  $R_{24}$ ,  $R_e$ ,  $R_f$ , and  $p$  are defined as above and an O-nitrosated imide is representative of the  $R_{25}$  group as defined above may be prepared as outlined in Figure 28. The amide of the formula **36** is converted to the imide of the formula **VIIC** wherein  $p$ ,  $R_e$  and  $R_f$  are defined as above by reaction with an appropriate nitrate containing activated acylating agent. Preferred methods for the formation of esters are reacting the alcohol with the preformed acid chloride or symmetrical anhydride of the nitrate containing acid or condensing the alcohol and nitrate containing acid in the presence of a dehydrating agent such as DCC or EDAC · HCl with a catalyst such as DMAP.

2-Hydroxy-2-nitrosohydrazine compounds of formula (**VII**) wherein  $R_{23}$ ,  $R_{24}$ ,  $R_e$ ,  $R_f$ ,  $R_i$ , and  $p$  are defined as above and a 2-hydroxy-2-nitrosohydrazine imide is representative of the  $R_{25}$  group as defined above may be prepared as outlined in Figure 29. The amide of the formula **36** is converted to the imide of the formula **39** wherein  $p$ ,  $R_e$ ,  $R_f$ , and  $R_i$  are defined as above by reaction with an appropriate protected amino containing activated acylating agent wherein  $P^3$  is as defined above. Preferred methods for the formation of imides are reacting the amide with the preformed acid chloride or symmetrical anhydride of the protected amino containing acid or condensing the alcohol and protected amine containing acid in the presence of a dehydrating agent such as DCC or EDAC · HCl with a catalyst such as DMAP. Preferred protecting groups for the amine are as a carbamate such as a t-butyl carbamate or a 9-fluorenylmethyl carbamate. Deprotection of the amino moiety (strong acid such as HCl in dioxane or trifluoroacetic acid is used to remove a t-butyl carbamate while piperidine is used to remove 9-fluorenylmethyl carbamate) followed by treatment of the amine with nitric oxide (1-5 atmospheres) in a dry inert solvent such as ether or tetrahydrofuran affords the compound of the formula **VIID**.

As noted above, another aspect the invention provides a composition comprising (i) a therapeutically effective amount of a steroid, a  $\beta$ -agonist, an

naturally susceptible or artificially provided binding sites for nitric oxide or derivatives which donate or release NO.

One group of such NO adducts is the S-nitrosothiols, which are compounds that include at least one -S-NO group. Such compounds include S-nitroso-polypeptides (the term "polypeptide" includes proteins and also polyamino acids that do not possess an ascertained biological function, and derivatives thereof); S-nitrosylated amino acids (including natural and synthetic amino acids and their stereoisomers and racemic mixtures and derivatives thereof); S-nitrosylated sugars, S-nitrosylated- modified and unmodified oligonucleotides (preferably of at least 5, and more particularly 5-200, nucleotides); and an S-nitrosylated hydrocarbons where the hydrocarbon can be a branched or unbranched, and saturated or unsaturated aliphatic hydrocarbon, or an aromatic hydrocarbon; S-nitrosylated hydrocarbons having one or more substituent groups in addition to the S-nitroso group; and heterocyclic compounds. S-nitrosothiols and the methods for preparing them are described in U.S. Patent No. 5,380,758; Oae *et al.*, *Org. Prep. Proc. Int.*, 15(3):165-198 (1983); Loscalzo *et al.*, *J. Pharmacol. Exp. Ther.*, 249(3):726729 (1989) and Kowaluk *et al.*, *J. Pharmacol. Exp. Ther.*, 256:1256-1264 (1990), all of which are incorporated in their entirety by reference.

One particularly preferred embodiment of this aspect relates to S-nitroso amino acids where the nitroso group is linked to a sulfur group of a sulfur-containing amino acid or derivative thereof. For example, such compounds include the following: S-nitroso-N-acetylcysteine, S-nitroso-captopril, S-nitroso-homocysteine, S-nitroso-cysteine and S-nitroso-glutathione.

Suitable S-nitrosylated proteins include thiol-containing proteins (where the NO group is attached to one or more sulfur group on an amino acid or amino acid derivative thereof) from various functional classes including enzymes, such as tissue-type plasminogen activator (TPA) and cathepsin B; transport proteins, such as lipoproteins, heme proteins such as hemoglobin and serum albumin; and biologically protective proteins, such as the immunoglobulins and the cytokines. Such nitrosylated proteins are described in PCT Publ. Applic. No. WO 93/09806, published May 27, 1993. Examples include polynitrosylated albumin where multiple thiol or other nucleophilic centers in the protein are modified.

hydrocarbons having one or more substituent groups in addition to the ON-N- or ON-C- group; and ON-N- or ON-C-heterocyclic compounds.

Another group of such NO adducts is the nitrites which have an -O-NO group wherein the organic template to which the nitrite group is appended is a protein, polypeptide, amino acid, carbohydrate, branched or unbranched and saturated or unsaturated alkyl, aryl or a heterocyclic compound. A preferred example is the nitrosylated form of isosorbide. Compounds in this group form S-nitrosothiol intermediates *in vivo* in the recipient human or other animal to be treated and can therefore include any structurally analogous precursor R-O-NO of the S-nitrosothiols described above.

Another group of such adducts are nitrates which donate, transfer or release nitric oxide and are selected from the group consisting of compounds that include at least one at least one O<sub>2</sub>N-O-, O<sub>2</sub>N-N-, O<sub>2</sub>N-S- or O<sub>2</sub>N-C- group. Preferred among these are those selected from the group consisting of O<sub>2</sub>N-O-, O<sub>2</sub>N-N-, O<sub>2</sub>N-S- or O<sub>2</sub>N-C-polypeptides; O<sub>2</sub>N-O-, O<sub>2</sub>N-N-, O<sub>2</sub>N-S- or O<sub>2</sub>N-C-amino acids; O<sub>2</sub>N-O-, O<sub>2</sub>N-N-, O<sub>2</sub>N-S- or O<sub>2</sub>N-C-sugars; O<sub>2</sub>N-O-, O<sub>2</sub>N-N-, O<sub>2</sub>N-S- or O<sub>2</sub>N-C-modified and unmodified oligonucleotides; O<sub>2</sub>N-O-, O<sub>2</sub>N-N-, O<sub>2</sub>N-S- or O<sub>2</sub>N-C- hydrocarbons which can be branched or unbranched, saturated or unsaturated aliphatic hydrocarbons or aromatic hydrocarbons; O<sub>2</sub>N-O-, O<sub>2</sub>N-N-, O<sub>2</sub>N-S- or O<sub>2</sub>N-C- hydrocarbons having one or more substituent groups in addition to the O<sub>2</sub>N-O-, O<sub>2</sub>N-N-, O<sub>2</sub>N-S- or O<sub>2</sub>N-C-group; and O<sub>2</sub>N-O-, O<sub>2</sub>N-N-, O<sub>2</sub>N-S- or O<sub>2</sub>N-C-heterocyclic compounds. Preferred examples are isosorbide dinitrate and isosorbide mononitrate.

Another group of such NO adducts is the nitroso-metal compounds which have the structure (L)<sub>u</sub>-M-(NO)<sub>v</sub>-A<sub>z</sub>. M is a metal, preferably a transition metal; L includes any appropriate organic or inorganic ligand directly attached to the metal; u, v, z are each integers independently selected from 1 to 5; and A is an appropriate organic or inorganic counterion to yield a neutral species. Preferred metals include iron, copper, manganese, cobalt, selenium and lutidium. A preferred example is sodium nitroprusside.

When administered *in vivo*, the nitric oxide adduct may be administered in combination with pharmaceutical carriers and in dosages described herein.

The instant disclosure, particularly in combination with the significant body of literature, commercially available pharmaceutically acceptable liquid, solid and gaseous carriers and vehicles, volume expanders, tableting and encapsulation materials, enteric and other coatings, and inhalant and intranasal delivery devices and the ordinary skill of those practicing in the field, amply teaches the reader how to use the compounds and compositions of the invention in the methods of the invention and particularly for oral and nasal inhalation and intranasal therapy. The following is supplementary to and exemplary thereof.

The pharmaceutical compositions utilized in this invention can be administered preferably by inhalation(oral and/or nasal), and also by intranasal mucosal administration, oral, enteral, topical, vaginal, sublingual, rectal, intramuscular, intravenous, or subcutaneous means.

The compounds of this invention can be employed in combination with conventional excipients; *i.e.*, pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral, enteral or intranasal application which do not deleteriously react with the active compounds. Suitable pharmaceutically acceptable carriers include, but are not limited to, water, salt solutions, alcohol, vegetable oils, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, petroethral fatty acid esters, hydroxymethylcellulose, polyvinylpyrrolidone, *etc.* The pharmaceutical preparations can be sterilized and if desired, mixed with auxiliary agents, *e.g.*, lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavoring and/or aromatic substances and the like which do not deleteriously react with the active compounds.

Many therapeutically active ingredients have been administered or applied to the body by means of inhalation, such as in aerosol dosage form. One of the main reasons for the rapid and widespread acceptance of the inhalation dosage forms for the administration of therapeutically active agents is that it affords many and

For enteral application, particularly suitable are tablets, dragees or capsules having talc and/or a carbohydrate carrier binder or the like, the carrier preferably being lactose and/or corn starch and/or potato starch. A syrup, elixir or the like can be used wherein a sweetened vehicle is employed. Sustained release compositions can be formulated including those wherein the active component is protected with differentially degradable coatings, e.g., by microencapsulation, multiple coatings, etc.

The nitrosated or nitrosylated compounds of the invention are used at dose ranges and over a course of dose regimen and are administered in the same or substantially equivalent vehicles/carrier by the same or substantially equivalent oral or nasal inhalant devices as their non-nitrosated or non-nitrosylated counterparts. The nitrosated or nitrosylated compounds of the invention can also be used in lower doses and in less extensive regimens of treatment. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex, diet and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination. Thus, the dosage regimen actually employed may vary widely and therefore may deviate from the preferred dosage regimen set forth above.

Total daily dose administered to a host in single or divided doses may be in amounts, for example, from about 1 to about 100 mg/kg body weight daily and more usually about 3 to 30 mg/kg. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more



### Example 1

#### 6 $\alpha$ -Fluoro-11 $\beta$ -hydroxy-16 $\alpha$ ,17-[(1-methylethylidene)bis(oxy)]pregna-1,4-diene--3,20-dione-21-(3-methyl-3-nitrosothio)-butanoate

##### 1a. 3-Methyl-3-(2,4,6-trimethoxyphenylmethylthio)butyric acid

To a solution of 3-mercapto-3-methylbutyric acid (B.J. Sweetman et al. *J. Med Chem.*, **14**, 868 (1971)) (4.6 g, 34 mmol) in methylene chloride (250 mL) under nitrogen and cooled over ice/salt to 5 °C (internal temperature) was added trifluoroacetic acid (82 g, 0.72 mol). No significant temperature rise was noted during the addition. To this was then added dropwise a solution of 2,4,6-trimethoxybenzyl alcohol (M.C. Munson et al., *J. Org. Chem.*, **57**, 3013 (1992)) (6.45 g, 32 mmol) in methylene chloride (150 mL) such that the reaction temperature does not rise above 5 °C. After the addition was complete, the mixture was stirred for an additional 5 minutes at 5 °C and the volatiles were removed *in vacuo* (toluene or ethyl acetate can be used to assist in the removal of volatile material). The residue was partitioned between diethyl ether and water and the organic phase dried over anhydrous sodium sulfate, filtered and the volatile material removed *in vacuo*. The residue was treated with activated charcoal and recrystallised from diethyl ether/hexane. The product was isolated as a white solid in 70% yield (7 g) mp 103- 105 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  6.12 (s, 2H), 3.80-3.85 (m, 11 H), 2.74 (s, 2H), 1.47 (s, 6H). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  173.9, 160.6, 158.6, 105.6, 90.5, 55.7, 55.3, 45.9, 43.6, 28.4, 21.0.

##### 1b. 6 $\alpha$ -Fluoro-11 $\beta$ -hydroxy-16 $\alpha$ ,17-[(1-methylethylidene)bis(oxy)]pregna-1,4-dien-3,20-dione-21-[3-methyl-3-(2,4,6-trimethoxyphenylmethylthio)]-butanoate

A solution 6 $\alpha$ -fluoro-11 $\beta$ , 21-dihydroxy-16 $\alpha$ ,17 $\alpha$ -[(1-methylethylidene)bis(oxy)]pregna-1,4-diene--3,20-dione (357 mg, 0.8 mmol), the compound of Example 1a (251 mg, 0.8 mmol) and 4-dimethylaminopyridine (20 mg, 0.16 mmol) in anhydrous DMF (5 mL) was treated with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (157 mg, 0.8 mmol). The resultant solution was stirred at room temperature for 2 hours when the solvent was removed *in vacuo* and the residue poured into water and extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. The residue was chromatographed on silica gel using ethyl acetate:hexane (1:1) The product was isolated as a solid in 41% yield (240 mg).

chloride (1:25). The product was isolated as a green solid 40 mg (65 %).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.12 (d,  $J=10$  Hz, 1H), 6.26 (s, 1H), 6.25 (d,  $J=10$  Hz, 1H), 5.30 (ddd,  $J=50$  Hz, 10 Hz, 6 Hz), 4.91-4.94 (m, 1H), 4.88 (d,  $J=18$  Hz, 1H), 4.78 (d,  $J=18$  Hz, 1H), 4.41-4.47 (m, 1H), 3.33 (s, 2H), 2.38-2.47 (m, 1H), 2.10-2.20 (m, 1H), 1.99 (s, 3H), 1.97 (s, 3H), 1.36 (s, 6H), 1.04-1.75 (m, 8H), 1.15 (s, 3H), 0.86 (s, 3H).

### Example 2

#### (8r)-3 $\alpha$ -hydroxy-8-isopropyl-1 $\alpha$ H,5 $\alpha$ H-tropanium nitrite (+)-tropate

(8r)-3 $\alpha$ -hydroxy-8-isopropyl-1 $\alpha$ H,5 $\alpha$ H-tropanium bromide ( $\pm$ )-tropate (0.2 g, 0.48 mmol) was dissolved in hot water (2 mL) and to it was added a solution of silver nitrite (75 mg, 0.48 mmol) in boiling water (2 mL). The solution was stirred for 5 min. while keeping the solution hot and then centrifuged at 1000 rpm for 5 min. The supernatant was decanted and the water was removed by lyophilisation. The residue was recrystallised from ethyl acetate/isopropanol to give the title compound as a white solid 124 mg (70%) mp 169-172  $^{\circ}\text{C}$  (dec).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  7.15-7.30 (m, 5H), 4.90 (t,  $J=5.5$  Hz, 1H), 3.97-4.04 (m, 1H), 3.65-3.82 (m, 4H), 3.55-3.62 (m, 1H), 2.56 (s, 3H), 2.28-2.5 (m, 2H), 1.75-2.1 (m, 4H), 1.57 (d,  $J=17$  Hz, 1H), 1.40-1.50 (m, 1H), 1.06-1.14 (m, 6H).  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  16.36, 24.46, 24.73, 31.25, 54.53, 55.18, 63.31, 65.20, 65.30, 127.82, 128.47, 129.00, 136.48, 171.64. Anal calcd for  $\text{C}_{20}\text{H}_{30}\text{N}_2\text{O}_5$ : C: 63.47; H: 7.99; N: 7.40. Found: C: 63.28; H: 7.92; N: 7.24.

### Example 3

#### (8r)-3 $\alpha$ -hydroxy-8-isopropyl-1 $\alpha$ H,5 $\alpha$ H-tropanium nitrate (+)-tropate

(8r)-3 $\alpha$ -hydroxy-8-isopropyl-1 $\alpha$ H,5 $\alpha$ H-tropanium nitrate ( $\pm$ )-tropate (0.2 g, 0.48 mmol) was dissolved in ethanol (2 mL) and to it added a solution of silver nitrate (82 mg, 0.48 mmol) in water (2 mL). The solution was stirred at room temperature for 1.5 hr. and centrifuged at 1000 rpm for 5 min. The supernatant was decanted and the volatile materials removed by lyophilisation. The product was recrystallised from isopropanol to give the title compound as a white solid 150 mg (76%) mp 180-182  $^{\circ}\text{C}$ .  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  7.21-7.39 (m, 5H), 5.03 (t,  $J=5.7$  Hz, 1H), 4.07-4.16 (m, 1H), 3.78-3.94 (m, 4H), 3.59-3.65 (m, 1H), 2.68 (s, 3H), 2.4-2.6 (m, 2H), 1.9-2.22 (m, 3H), 1.91 (d,  $J=17.2$  Hz, 1H), 1.69 (d,  $J=17.2$  Hz, 1H), 1.49-1.59 (m, 1H), 1.06-1.14 (t,  $J=6$  Hz, 6H).  $^{13}\text{C}$  NMR

washed with methanol. The filtrate was reduced *in vacuo* and the residue chromatographed on silica gel using ethyl acetate:hexane (1:1) to give the product as a white solid. mp. 211-213 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.26 (d, J=10 Hz, 1H), 6.35 (d, J=10 Hz, 1H), 6.14 (s, 1H), 4.95 (dd, J=50 Hz, 17 Hz), 4.99 (d, J=4.6 Hz, 1H), 4.56 (t, J=6.2 Hz, 2H), 4.43 (d, J=8.5 Hz, 1H), 2.33-2.75 (m, 7H), 2.04-2.18 (m, 3H), 1.84-1.95 (m, 1H), 1.55-1.75 (m, 3H), 1.56 (s, 3H), 1.44 (s, 3H), 1.22 (s, 3H), 0.94 (s, 3H). Anal calcd for C<sub>28</sub>H<sub>36</sub>FNO<sub>10</sub>: C, 59.46; H, 6.42. Found: C, 59.26; H, 6.34.

### Example 5

#### 9-Fluoro-11β-hydroxy-16α,17α-[(1-methylethylidene)bis(oxy)]pregna-1,4-diene--3,20-dione-21-(12-nitrosooxy)-dodecanoate

##### 5a. 9-Fluoro-11β-hydroxy-16α,17α-[(1-methylethylidene)bis(oxy)]pregna-1,4-diene--3,20-dione-21-(12-*tert*-butyldimethylsilyloxy)-dodecanoate

A solution of 9-Fluoro-11β, 21-dihydroxy-16α,17α-[(1-methylethylidene)bis(oxy)]pregna-1,4-diene--3,20-dione (1 g, 2.3 mmol) and 12-*tert*-butyldimethylsilyloxydodecanoic acid (760 mg, 2.3 mmol) [*J. Org. Chem.*, 50, 1616 (1985)] in dry DMF (10 mL) was stirred at room temperature under nitrogen and 4-DMAP (56 mg, 0.46 mmol) added followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (528 mg, 2.8 mmol). The resultant solution was stirred overnight at room temperature and the solvent removed *in vacuo*. The residue was chromatographed on silica gel using ethyl acetate:hexane (1:3 then 1:1) to give the product as a white solid 1.1 g (70 % based on recovered starting material). mp. 146-148 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.16 (d, J=10 Hz, 1H), 6.30 (d, J=10 Hz, 1H), 6.09 (s, 1H), 4.94 (d, J=4.9 Hz, 1H), 4.86 (d, J=6.9 Hz), 4.37 (d, J=8.6 Hz, 1H), 3.55 (t, J=6.5 Hz, 2H), 2.59 (m, 1H), 2.32-2.45 (m, 6H), 2.04-2.15 (m, 1H), 1.68-1.78 (m, 1H), 1.2-1.7 (21 H), 1.50 (s, 3H), 1.38 (s, 3H), 1.17 (s, 3H), 0.89 (s, 3H), 0.84 (s, 9H), 0.00 (s, 6H).

##### 5b. 9-Fluoro-11β-hydroxy-16α,17α-[(1-methylethylidene)bis(oxy)]pregna-1,4-diene--3,20-dione-21-(12-hydroxy)-dodecanoate

The product of Example 5a (0.15 g, 0.2 mmol) was dissolved in THF (1.3 mL) and trifluoroacetic acid (160 μL) added followed by water (40 μL). The resultant solution was stirred at room temperature for 1 hr, the volatile material removed *in vacuo* and the residue chromatographed on silica gel using ethyl

*tert*- Butyl nitrite (248  $\mu$ L, 215 mg, 2.09 mmol) was introduced and the resultant solution stirred at room temperature for 25 min when the solvent was removed *in vacuo* at room temperature. The green gum was stirred with ether collecting the resultant solid by filtration (225 mg, 97 %).  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  13.21 (br s, 1H), 8.54 (d,  $J=9.45$  Hz, 1H), 5.18 (d,  $J=5.46$  Hz, 1H), 1.98 (s, 3H), 1.95 (s, 3H), 1.88 (s, 3H).

6b. 2-(*tert*-Butylamino-1-(4-hydroxy-3-hydroxymethylphenyl)ethanol 2(R,S)-acetamido-3-methyl-3-nitrosothiol propionic acid salt

2-(*tert*-Butylamino-1-(4-hydroxy-3-hydroxymethylphenyl)ethanol 25 mg, 0.1 mmol) and the product of Example 6a (23 mg, 0.1 mmol) were stirred in water to homogeneity then lyophilised to dryness to give the salt (48 mg, 100 %) mp 180-182  $^{\circ}\text{C}$ .  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  9.38 (br s, 1H), 7.81 (d,  $J=9.34$  Hz, 1H), 7.33 (s, 1H), 7.08 (d,  $J=8.2$  Hz, 1H), 6.75 (d,  $J=8.2$  Hz, 1H), 4.98 (br s, 1H), 4.69 (d,  $J=9.2$  Hz, 1H), 2.72-2.95 (m, 2H), 1.97 (s, 3H), 1.94 (s, 3H), 1.86 (s, 3H), 1.23 (s, 9H).  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  172.52, 169.33, 154.07, 132.63, 128.60, 125.41, 125.29, 114.63, 69.16, 61.45, 60.77, 58.61, 55.54, 48.91, 27.36, 26.21, 25.63, 23.04. Anal calcd for  $\text{C}_{20}\text{H}_{33}\text{N}_3\text{O}_7\text{S}$ : C, 52.27; H, 7.23; N, 9.14. Found: C, 52.49; H, 7.33; N, 8.85.

### Example 7

5,5 $\ddot{\text{O}}$ -(2-Hydroxy-1,3-propanediyl)bis-(oxy)]bis[4-oxo-4H-1benzopyran-2(4-nitrooxybutyl)-carboxylic acid ester

7a. 5,5 $\ddot{\text{O}}$ -(2-Hydroxy-1,3-propanediyl)bis-(oxy)]bis[4-oxo-4H-1benzopyran-2(4-bromobutyl)-carboxylic acid ester

5,5 $\ddot{\text{O}}$ -(2-Hydroxy-1,3-propanediyl)bis-(oxy)]bis[4-oxo-4H-1benzopyran-2-carboxylic acid disodium salt (2.6 g, 5.07 mmol) and 1,4-dibromobutane (8.7 g, 40.6 mmol) were stirred at room temperature in DMSO for 72 hr and then the solvent removed by vacuum distillation. The residue was diluted with  $\text{CH}_2\text{Cl}_2$  and washed with water. The aqueous phase was extracted once with  $\text{CH}_2\text{Cl}_2$  and the combined extracts washed with brine and dried over sodium sulfate. The solution was filtered, the solvent removed *in vacuo* and the residue chromatographed on silica gel using ethyl acetate:hexane (4:1) to give cromolyn bis(4- ester) as a solid 1.2 g (32 %). mp 130-133  $^{\circ}\text{C}$ .  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  7.74 (t,  $J=8.4$  Hz, 2H), 7.16 (dd,  $J=18.6$  Hz, 8.4 Hz, 4H), 6.73 (s, 2H), 5.37 (br. s, 1H), 4.29-4.40 (m, 9H), 3.63 (t,  $J=6.3$  Hz, 4H), 1.83-2.03 (m, 8H).  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$

(s, 6H), 1.40 (s, 18H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  177.95, 170.52, 167.32, 160.32, 158.69, 157.53, 155.16, 150.35, 134.86, 116.17, 115.51, 111.03, 109.54, 85.08, 79.78, 70.22, 67.63, 66.08, 64.39, 59.88, 51.14, 28.17, 28.12, 27.80, 25.32, 25.05, 25.01

8b. 5,5 $\bar{\text{O}}$ -[(2-Hydroxy-1,3-propanediyl)bis-(oxy)]bis[4-oxo-4H-1benzopyran-2(4-  
(2(S)-acetamido -3-methyl-3-mercapto) propionic acid butyl)-carboxylic  
acid ester

The product of Example 8a (0.62 mg, 0.49 mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (9 mL) and anisole (450 mg) added followed by trifluoroacetic acid (10 mL). The resultant solution was stirred at room temperature for 2 hr when the volatiles were removed *in vacuo*. The residue was dissolved in more  $\text{CH}_2\text{Cl}_2$  (9 mL) and stirred over ice under nitrogen. After 10 minutes triethylamine (286  $\mu\text{L}$ , 206 mg, 2.04 mmol) was introduced followed by acetyl chloride (76  $\mu\text{L}$ , 84 mg, 1.07 mmol). The resultant solution was stirred overnight at room temperature, washed with 0.5N HCl, dried over  $\text{Na}_2\text{SO}_4$ , filtered and the solvent removed *in vacuo*. The residue was chromatographed on silica gel using ethyl acetate:hexane (9:1) then ethyl acetate:methanol (9:1) to give the product as a foam 120 mg (30 %).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.54 (t, J=8.4 Hz, 2H), 7.08 (d, J=8.4, 2H), 6.90 (d, J=8.3 Hz, 2H), 6.87 (s, 2H), 6.57 (d, J=9.2 Hz, 2H), 4.58 (d, J=9.2 Hz, 2H), 4.15-4.55 (m, 13H), 2.01 (s, 6H), 1.96 (s, 2H), 1.75-1.9 (s, 8H), 1.44 (s, 6H), 1.31 (s, 6H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  177.88, 170.30, 169.91, 160.18, 158.51, 157.37, 150.15, 134.84, 116.02, 115.25, 110.83, 109.29, 70.09, 67.46, 65.93, 64.44, 60.33, 46.10, 30.83, 29.29, 24.90, 24.88, 22.91.

8c. 5,5 $\bar{\text{O}}$ -[(2-Hydroxy-1,3-propanediyl)bis-(oxy)]bis[4-oxo-4H-1benzopyran-2(4-  
(2(S)-acetamido -3-methyl-3-nitrosothiol) propionic acid butyl)-carboxylic  
acid ester

The product of Example 8b (110 mg, 0.11 mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (3 mL). To this was added tert butylnitrite (81  $\mu\text{L}$ , 70 mg, 0.69 mmol) and the resultant solution stirred at room temperature for 1 hr. The volatile material was removed *in vacuo* and the residue chromatographed on silica gel using ethyl acetate:acetone (4:1) to give the product as a foam 50 mg (43 %).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.61 (t, J=8.4 Hz, 2H), 7.17 (d, J=8.4 Hz, 2H), 6.90-7.08 (m, 4H), 6.40 (d, J=9.2 Hz, 2H), 5.35 (d, J=9.3 Hz, 2H), 4.1-4.65 (m, 13H), 2.07 (s, 6H), 2.04 (s, 6H), 1.95 (s, 6H), 1.73-1.88 (m, 8H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  178.06, 169.95, 169.90, 160.38, 158.76, 157.60, 150.35, 134.95, 116.27,

Each test drug was aerosolised to an animal 30 minutes prior to challenge with ascaris suum.

## RESULTS

Sheep were treated with 500 ug of either Example 1 or 6 $\alpha$ -fluoro-11 $\beta$ , 21-dihydroxy-16 $\alpha$ ,17 $\alpha$ -[(1-methylethylidene)bis(oxy)]pregna-1,4-diene--3,20-dione. Data are referenced to historical controls as described in the methods section. The data showed that Example 1 gave 59 $\pm$ 14 % protection of the immediate response and 89 $\pm$ 2 % protection of the peak late response (n=3). 6 $\alpha$ -Fluoro-11 $\beta$ , 21-dihydroxy-16 $\alpha$ ,17 $\alpha$ -[(1-methylethylidene)bis(oxy)]pregna-1,4-diene--3,20-dione gave 16 $\pm$ 21 % protection against the immediate response and 83 $\pm$ 7 % protection against the peak late response (n=3).

Measurement of airway hyperresponsiveness showed the post challenge/prechallenge ratios of PC150 values were 0.53 $\pm$ 0.10 (control) and 1.18 $\pm$ 0.06 (Example 1) and 0.59 $\pm$ 0.06 (control) and 0.98 $\pm$ 0.10 (6 $\alpha$ -fluoro-11 $\beta$ , 21-dihydroxy-16 $\alpha$ ,17 $\alpha$ -[(1-methylethylidene)bis(oxy)]pregna-1,4-diene--3,20-dione).

The results show that Example 1 provides a better protection against lung function changes due to aerosol challenge of ascaris suum in the conscious sheep.

It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

$T[C(R_y)(R_z)]_p$  wherein  $R_y$  and  $R_z$  are independently selected from  $-T^1-[C(R_e)(R_f)]_p-$   
 $G-[C(R_e)(R_f)]_p-T^2-Q$  wherein  $G$  is (i) a covalent bond; (ii)  $-T-C(O)-$ ; (iii)  $-C(O)-T$ ,  
 or (iv)  $Y$ , and wherein  $R_d$ ,  $R_e$ ,  $R_f$ ,  $p$ ,  $Q$ ,  $T$ , and  $Y$  are as defined above;

(2)  $-C(O)-C(O)-O-R_i$  wherein  $R_i$  is as defined above;

(3)  $-C(O)-B-R_i$  wherein  $B$  and  $R_i$  are as defined above;

(4)  $-C(O)-CH_2-B-C(O)-R_i$  wherein  $B$  and  $R_i$  are as defined above;

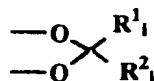
(5)  $-C(O)-CH_2-X$  wherein  $X$  is halogen;

(6)  $-S-R_i$  wherein  $R_i$  is as defined above;

(7)  $-C(O)CH_2-B-M$  wherein  $M$  is selected from  $-C(O)T-[C(R_e)(R_f)]_p-$   
 $G-[C(R_e)(R_f)]_p-N[N(O)N=O]-R_i$  or

$-C(R_d)-O-C(O)T-[C(R_e)(R_f)]_p-G-[C(R_e)(R_f)]_p-N[N(O)N=O]-R_i$  wherein  $R_e$ ,  $R_f$ ,  
 $R_i$ ,  $p$ ,  $G$  and  $T$  are as defined above;

$R_2$  and  $R_3$  are independently selected from hydrogen, hydroxyl, lower alkyl,  
 $-O(O)C-R_i$ , or  $-S-R_i$  wherein  $R_i$  is as defined above or  $R_2$  and  $R_3$  when taken  
 together are

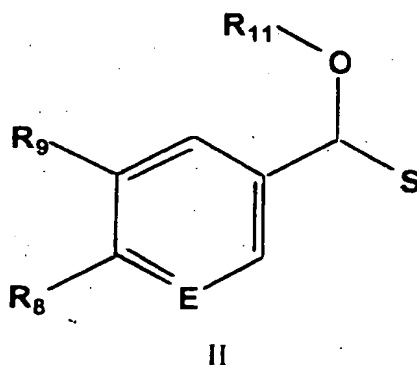


wherein  $R^1$  and  $R^2$  are independently selected from  $R_i$  wherein  $R_i$  is as defined  
 above;

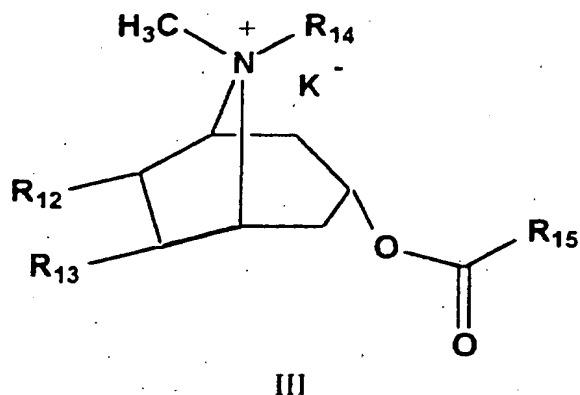
$R_4$  and  $R_5$  are independently selected from hydrogen or halogen;

$R_6$  is selected from hydrogen,  $D$ , or  $M$  wherein  $D$  and  $M$  are as defined above  
 with the provision that  $R_6$  must be  $D$  or  $M$  if the selection for  $R_1$  does not include  
 $D$  or  $M$ ;

(ii) compounds having the structure:



wherein,



wherein,

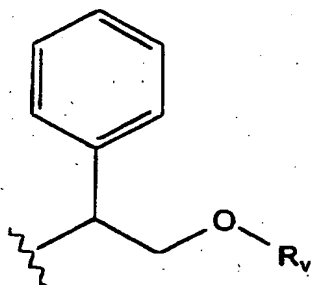
K is a monovalent anion selected from halide, nitrate, or nitrite;

R<sub>12</sub> and R<sub>13</sub> are hydrogen or, when taken together are oxygen;

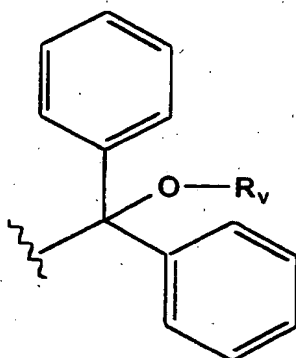
R<sub>14</sub> is lower alkyl or haloalkyl;

R<sub>15</sub> is selected from:

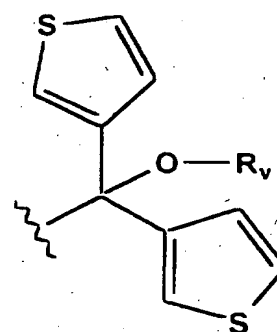
(i)



(ii)



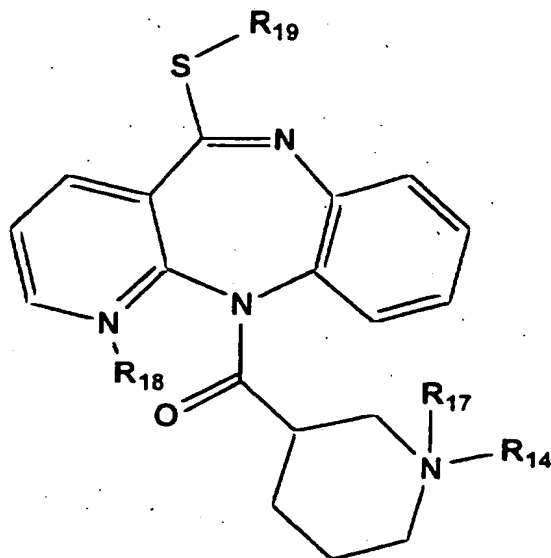
(iii)



wherein R<sub>v</sub> is selected from D or M and D and M are as defined above;

(iv) compounds having the structure:

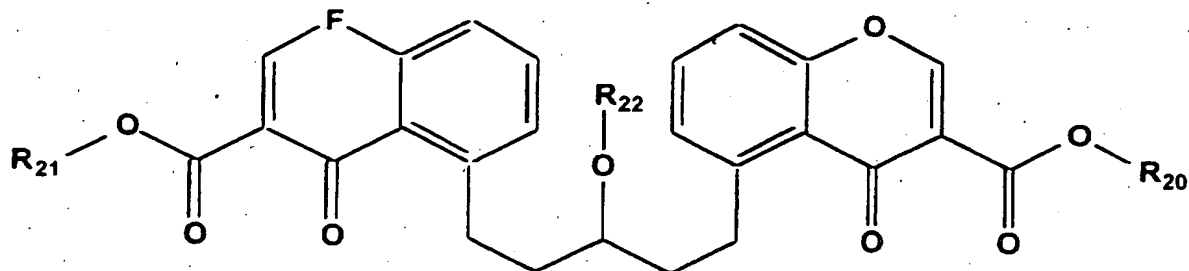




V

wherein  $R_{19}$  is selected from  $-[C(R_e)(R_f)]_p-G-[C(R_e)(R_f)]_p-T-Q$  or  $-S(O_2)-[C(R_e)(R_f)]_p-G-[C(R_e)(R_f)]_p-N[N-(O-)N=O]-R_i$  wherein  $R_e$ ,  $R_f$ ,  $R_i$ ,  $p$ ,  $G$ ,  $Q$  and  $T$  are as defined above; and wherein  $R_{14}$ ,  $R_{17}$ , and  $R_{18}$  are as defined above;

(vi) compounds having the structure:

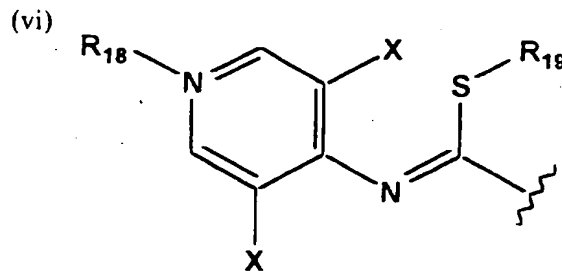
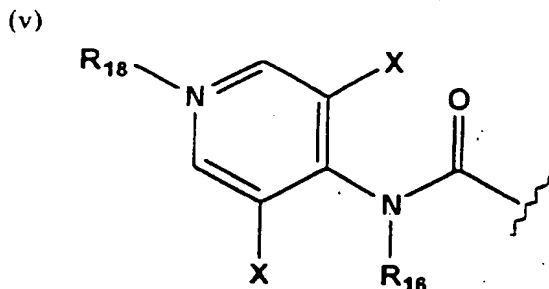


VI

wherein,

$F$  is selected from oxygen or  $NR_i$  wherein  $R_i$  is as defined above;

$R_{20}$  and  $R_{21}$  are independently selected from (1)  $-Y-[C(R_e)(R_f)]_p-H-[C(R_e)(R_f)]_p-T-Q$ ; wherein  $H$  is (i) a covalent bond; (ii)  $-T-C(O)-$ ; (iii)  $-C(O)-T$ ; (iv)  $-C(Y-C(O)-R_m)-$  wherein  $R_m$  is heteroaryl or heterocyclic ring; and wherein  $Y$ ,  $R_d$ ,  $R_e$ ,  $R_f$ ,  $p$ ,  $Q$  and  $T$  are as defined above; (2)  $T-[C(R_e)(R_f)]_p-H-[C(R_e)(R_f)]_p-N[N-(O-)N=O]-R_i$  wherein  $R_d$ ,  $R_e$ ,  $R_f$ ,  $R_i$ ,  $p$ ,  $H$  and  $T$  are as defined above; (3)



wherein X is halogen and  $R_{26}$  is selected from D or M and wherein  $R_{16}$ ,  $R_{18}$ , and  $R_{19}$  are defined as above.

3. A composition comprising (i) a therapeutically effective amount of a steroid, a  $\beta$ -agonist, an anticholinergic, a mast cell stabilizer or a PDE inhibitor and (ii) a compound that donates, transfers or releases nitric oxide or stimulates endogenous production of NO or EDRF *in vivo*.

4. The composition of claim 3 wherein

(i) the steroid is selected from the group consisting of beclomethasone, fluticasone, flunisolide, triamcinolone, butixocort, dexamethasone, fluocortin, budesonide, tixocortol, tipredane and mometasone;

(ii) the  $\beta$ -agonist is selected from the group consisting of salmeterol, albuterol, metaproterenol, terbutaline, pirbuterol, rimiterol, clenbuterol, bitolterol and reproterol;

(iii) the anticholinergic is selected from the group consisting of ipratropium, flutropium, tiotropium and rispenzepine;

(iv) the mast cell stabilizer is selected from the group consisting of cromolyn and nedocromil; and

(v) the PDE inhibitor is selected from the group consisting of tolafentrine, piclamilast, rolipram, flaminast, denbufylline, and zardaverine.

5. The composition of claim 3 wherein the compound that donates, transfers or releases nitric oxide is a S-nitrosothiol.

6. The composition of claim 5 wherein the S-nitrosothiol is selected from the group consisting of those having the structures:

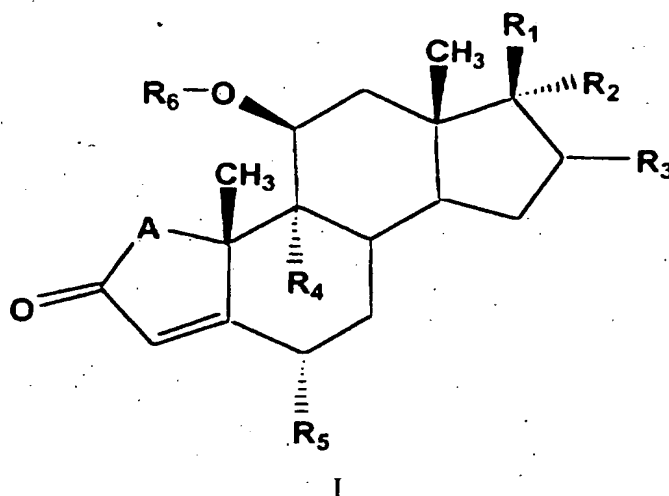
(i)  $\text{CH}_3[\text{C}(\text{R}_c)(\text{R}_f)]_x\text{SNO}$ ;

group or a group which stimulates endogenous synthesis of NO or EDRF *in vivo* and (ii) a compound that donates, transfers or releases nitric oxide or elevates endogenous synthesis levels of nitric oxide.

10. The composition of claim 9 wherein the steroid,  $\beta$ -agonist, anticholinergic, mast cell stabilizer or PDE inhibitor is a compound which has been linked through a site selected from the group consisting of oxygen, sulfur, carbon and nitrogen.

11. The composition of claim 9 wherein compound (i) is selected from the group consisting of:

(i) compounds having the structure:

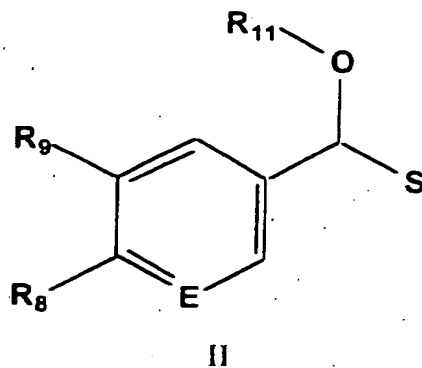


wherein

A is selected from  $-\text{CH}=\text{CH}-$  or  $-\text{CH}_2-\text{CH}_2-$ ;

$\text{R}_1$  is selected from

(1)  $-\text{C}(\text{O})\text{CH}_2-\text{B}-\text{D}$  wherein B is oxygen or sulfur; D is selected from (i)  $-\text{NO}$ ; (ii)  $-\text{NO}_2$ ; (iii)  $-\text{C}(\text{R}_d)-\text{O}-\text{C}(\text{O})-\text{Y}-[\text{C}(\text{R}_e)(\text{R}_f)]_p-\text{T}-\text{Q}$  in which  $\text{R}_d$  is hydrogen, lower alkyl, cycloalkyl, aryl, alkylaryl, aryl or heteroaryl, Y is oxygen, sulfur, or  $\text{NR}_i$  in which  $\text{R}_i$  is hydrogen, lower alkyl, lower haloalkyl, or heteroaryl,  $\text{R}_e$  and  $\text{R}_f$  are at each occurrence independently selected from hydrogen, lower



wherein,

E is nitrogen or C-R<sub>7</sub> wherein R<sub>7</sub> is hydrogen, halogen, -CH<sub>2</sub>O-R<sub>j</sub>, or -O-R<sub>j</sub> wherein R<sub>j</sub> is hydrogen, D or M wherein D and M are defined as above;

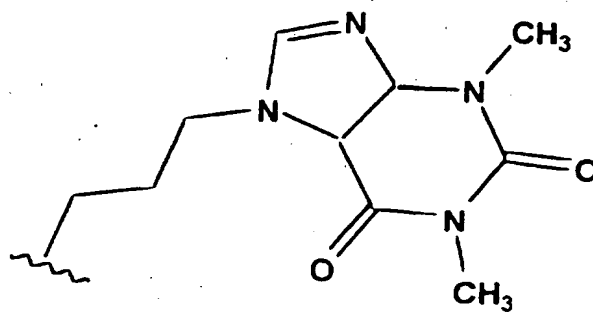
R<sub>8</sub> and R<sub>9</sub> are independently selected from amino, hydrogen, -CH<sub>2</sub>O-R<sub>j</sub>, or -O-R<sub>k</sub> wherein R<sub>k</sub> is -C(O)-R<sub>d</sub> or R<sub>j</sub> and R<sub>d</sub> and R<sub>j</sub> are as defined above;

S is (1) -CH<sub>2</sub>-N(Z)-R<sub>10</sub> wherein Z is hydrogen, -[N(O)N=O], or M wherein M is as defined above and R<sub>10</sub> is selected from

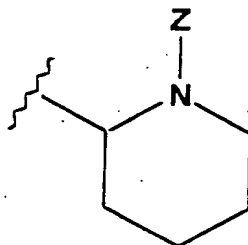
(i) lower alkyl

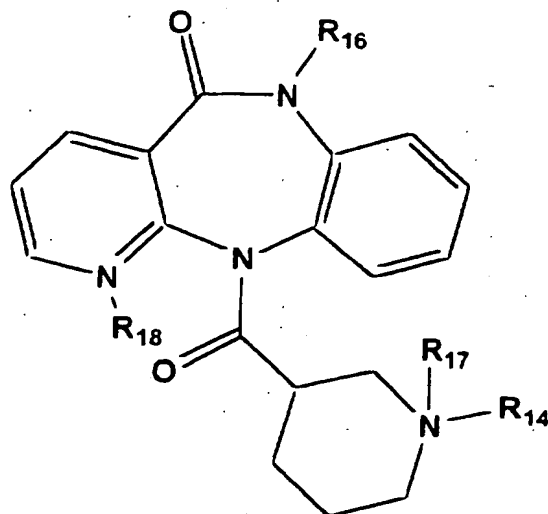
(ii) -(CH<sub>2</sub>)<sub>p</sub>-O-(CH<sub>2</sub>)<sub>a</sub>-C<sub>6</sub>H<sub>5</sub> wherein a is an integer from 1 to 4 and p is as defined above;

(iii)



(2)





IV

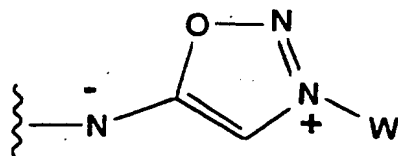
wherein

$R_{14}$  is as defined above;

$R_{16}$  is selected from hydrogen,  $-C(R_d)-O-C(O)-Y-[C(R_e)(R_f)]_p-T-Q$ ,  $-C(O)-T^1-[C(R_e)(R_f)]_p-T^2-Q$ , or M; and wherein  $R_d$ ,  $R_e$ ,  $R_f$ , M, p, T,  $T^1$ ,  $T^2$ , Q, and Y are defined as above; and

$R_{17}$  and  $R_{18}$  are independently selected from a lone pair of electrons,  $-C(R_d)-O-C(O)-Y-[C(R_e)(R_f)]_p-T-Q$ , or M wherein  $R_d$ ,  $R_e$ ,  $R_f$ , M, p, T, Q, and Y are defined as above with the provision that  $R_{17}$  and/or  $R_{18}$  must be  $-C(R_d)-O-C(O)-Y-[C(R_e)(R_f)]_p-T-Q$  or M when  $R_{16}$  is hydrogen;

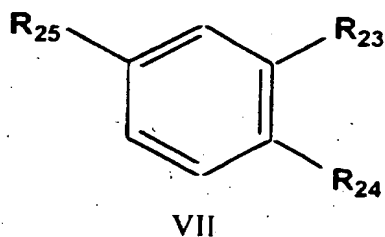
(v) compounds having the structure:



in which W is a heterocyclic ring or  $\text{NR}_s\text{R}'_s$  wherein  $\text{R}_s$  and  $\text{R}'_s$  are independently selected from lower alkyl, aryl or alkenyl; (4) sodium or (5) hydrogen;

$\text{R}_{22}$  is hydrogen, M, or D with the provision that  $\text{R}_{22}$  must be M or D when  $\text{R}_{20}$  and  $\text{R}_{21}$  are selected as sodium or hydrogen;

(vii) compounds having the structure:



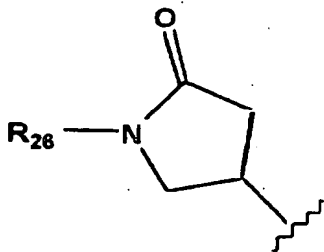
wherein,

$\text{R}_{23}$  is alkoxy, cycloalkoxy, or halogen;

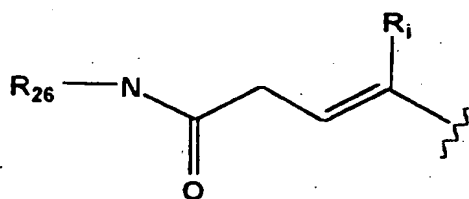
$\text{R}_{24}$  is hydrogen, alkoxy, or haloalkoxy; and

$\text{R}_{25}$  is selected from:

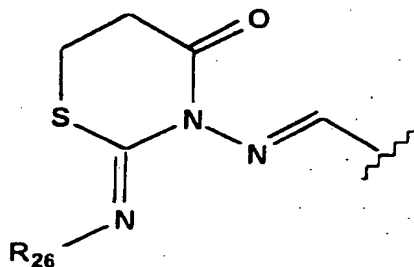
(i)



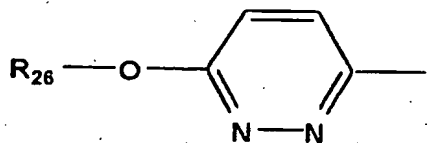
(ii)



(iii)



(iv)



- (i)  $\text{CH}_3[\text{C}(\text{R}_e)(\text{R}_f)]_x\text{SNO}$  ;
- (ii)  $\text{HS}[\text{C}(\text{R}_e)(\text{R}_f)]_x\text{SNO}$ ;
- (iii)  $\text{ONS}[\text{C}(\text{R}_e)(\text{R}_f)]_x\text{B}$ ; and
- (iv)  $\text{H}_2\text{N}-(\text{CO}_2\text{H})-(\text{CH}_2)_x-\text{C}(\text{O})\text{NH}-\text{C}(\text{CH}_2\text{SNO})-\text{C}(\text{O})\text{NH}-\text{CH}_2-\text{CO}_2\text{H}$

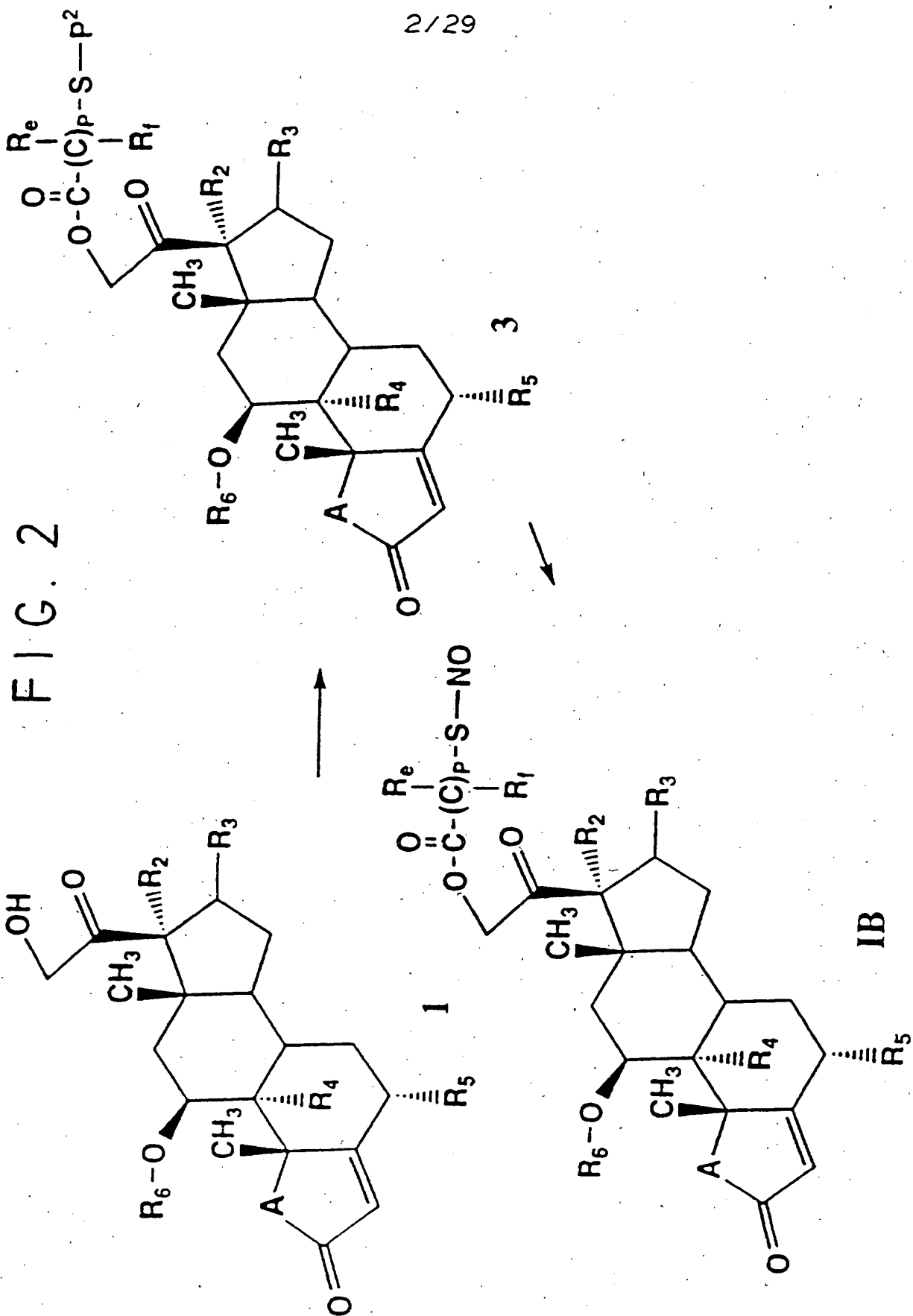
wherein x equals 2 to 20;  $\text{R}_e$  and  $\text{R}_f$  are independently selected from hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl, alkylamino, dialkylamino or taken together are carbonyl, cycloalkyl or bridged cycloalkyl; and B is selected from the group consisting of fluoro, alkoxy, cyano, carboxamido, cycloalkyl, arylkoxy, alkylsulfinyl, arylthio, alkylamino, dialkylamino, hydroxy, carbamoyl, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, amino, hydroxyl, carboxyl, hydrogen, nitro and aryl.

15. The composition of claim 13 wherein the compound that donates, transfers or releases nitric oxide is selected from the group consisting of:

- (i) compounds that include at least one ON-O-, ON-N- or ON-C- group;
- (ii) a N-oxo-N-nitrosoamine which has an  $\text{R}_{61}\text{R}_{62}-\text{N}(\text{O}-\text{M}^+)-\text{NO}$  group wherein  $\text{R}_{61}$  and  $\text{R}_{62}$  include polypeptides, amino acids, sugars, modified and unmodified oligonucleotides, hydrocarbons where the hydrocarbon can be a branched or unbranched, and saturated or unsaturated aliphatic hydrocarbon or an aromatic hydrocarbon, hydrocarbons having one or more substituent groups and heterocyclic compounds; and
- (iii) a thionitrate which has the structure  $\text{R}_{70}-\text{S}-\text{NO}_2$  wherein  $\text{R}_{70}$  includes polypeptides, amino acids, sugars, modified and unmodified oligonucleotides, and a hydrocarbon where the hydrocarbon can be a branched or unbranched, and saturated or unsaturated aliphatic hydrocarbon or an aromatic hydrocarbon; and
- (iv) a nitrate which has the structure  $\text{R}_{70}-\text{O}-\text{NO}_2$  wherein  $\text{R}_{70}$  is as defined above.

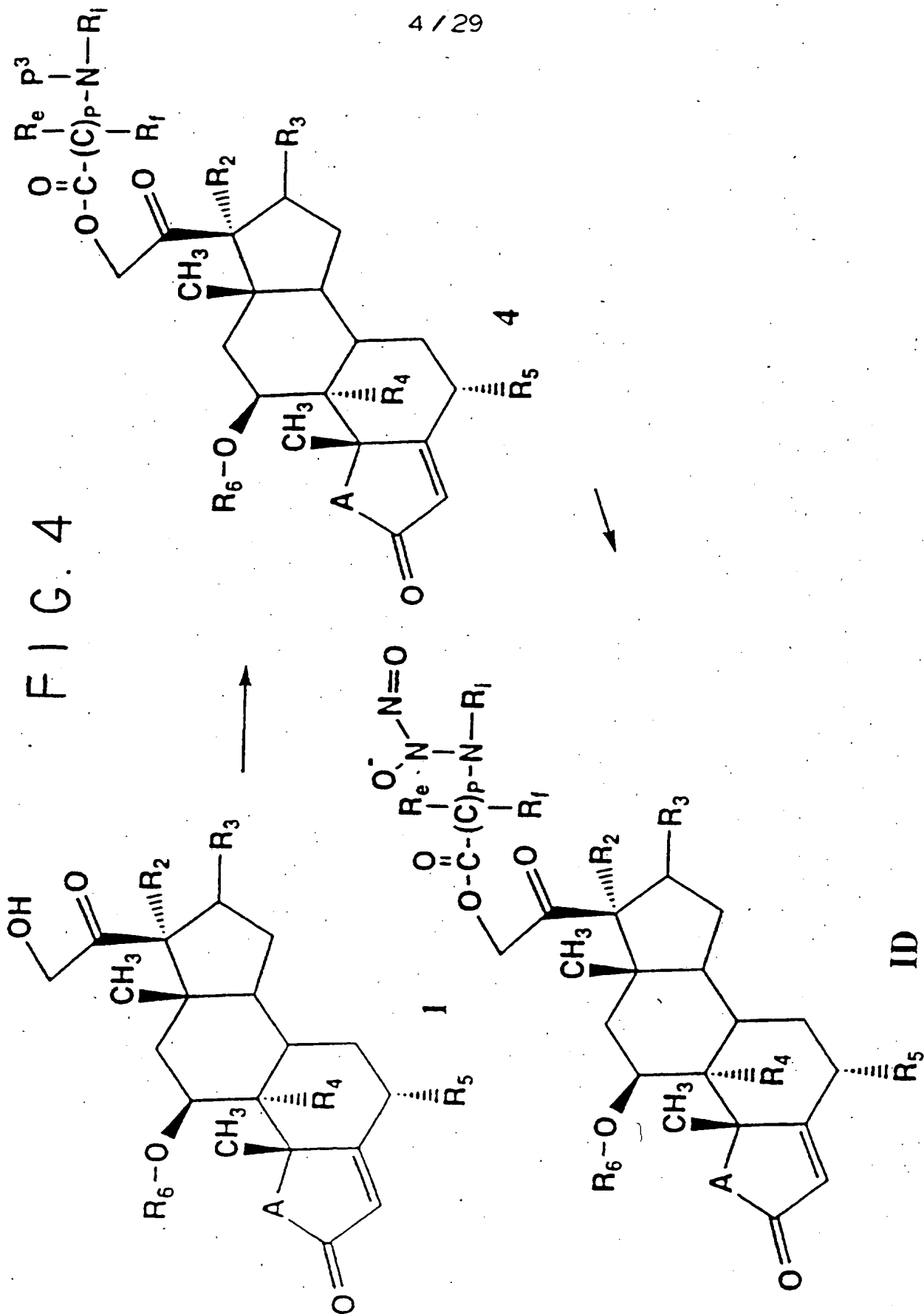
16. The composition of claim 9 wherein the compound that stimulates the endogenous production of NO or EDRF *in vivo* is selected from the group consisting of L-arginine, cytokines, adenosine, bradykinin, calreticulin, bisacodyl, phenolphthalein, and endothelin.

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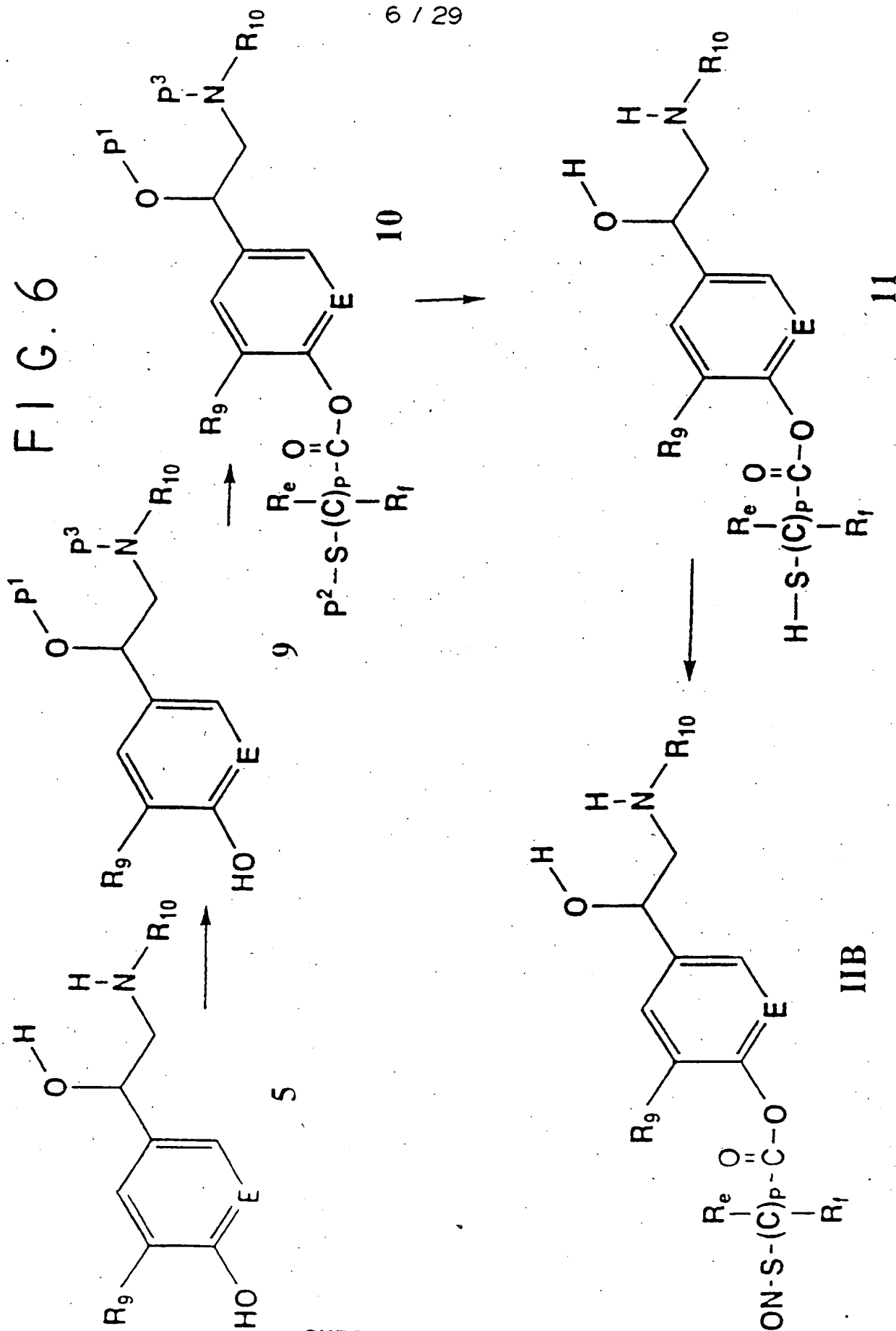


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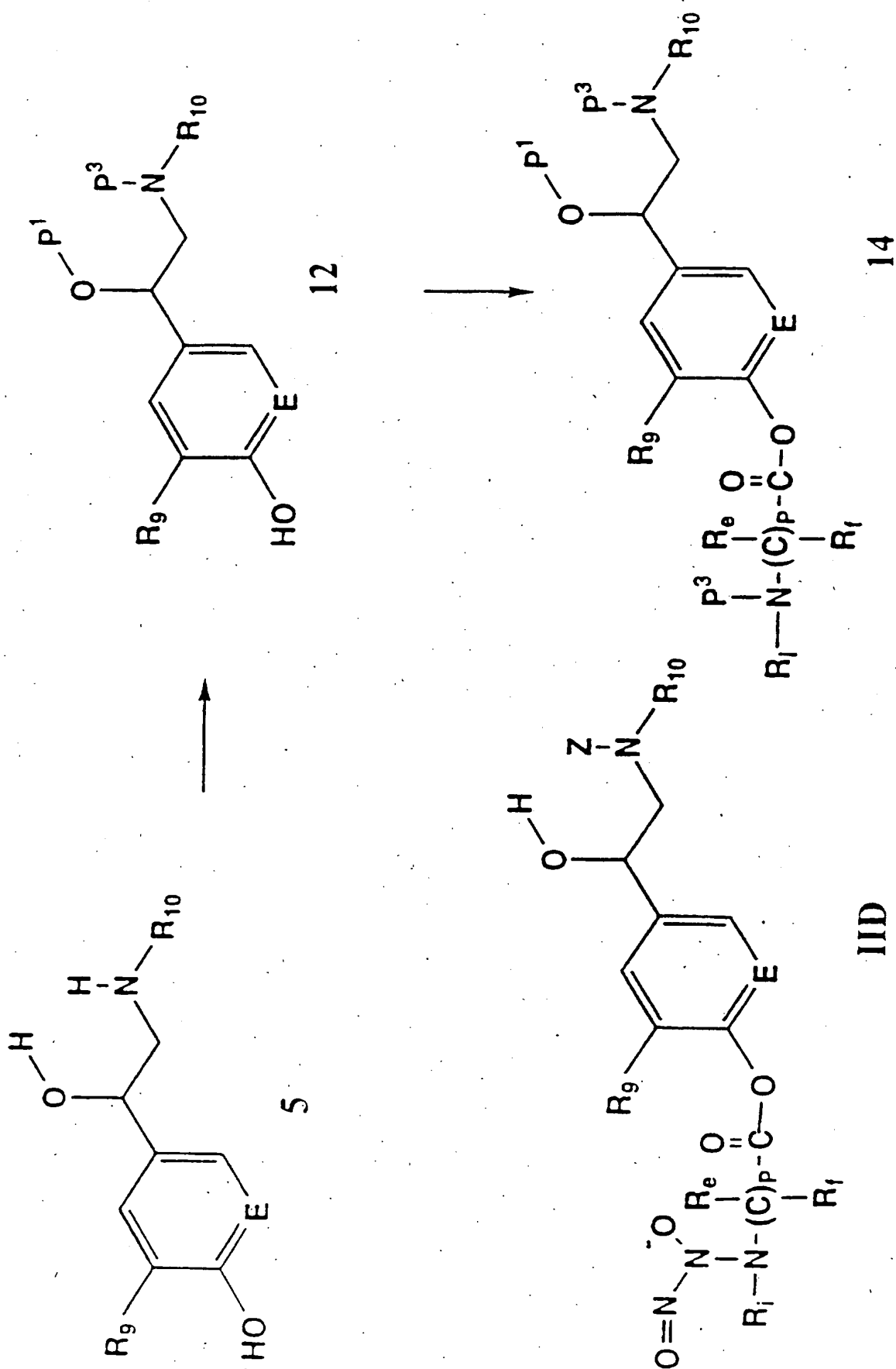
FIG. 6



SUBSTITUTE SHEET (RULE 26)

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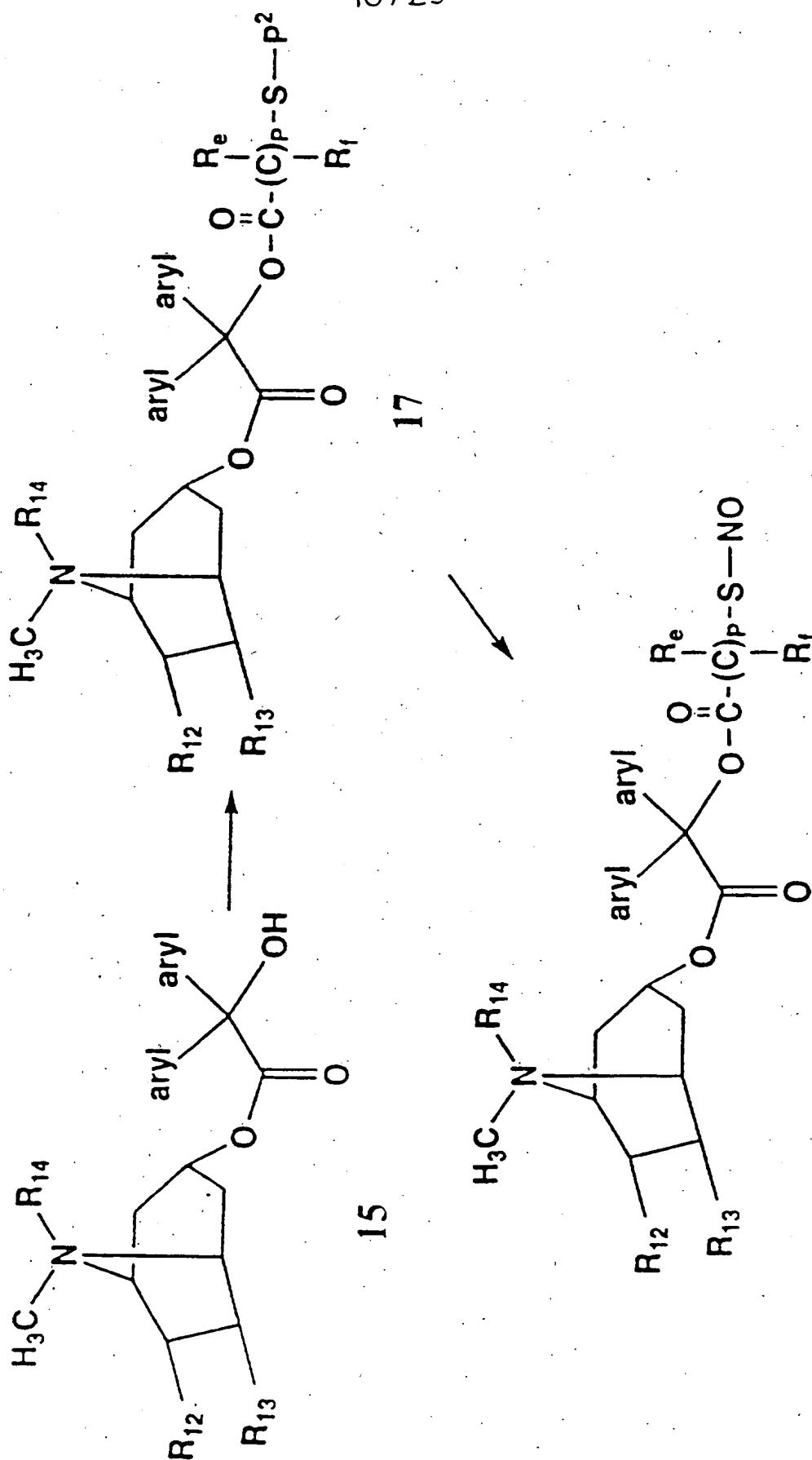
FIG. 8



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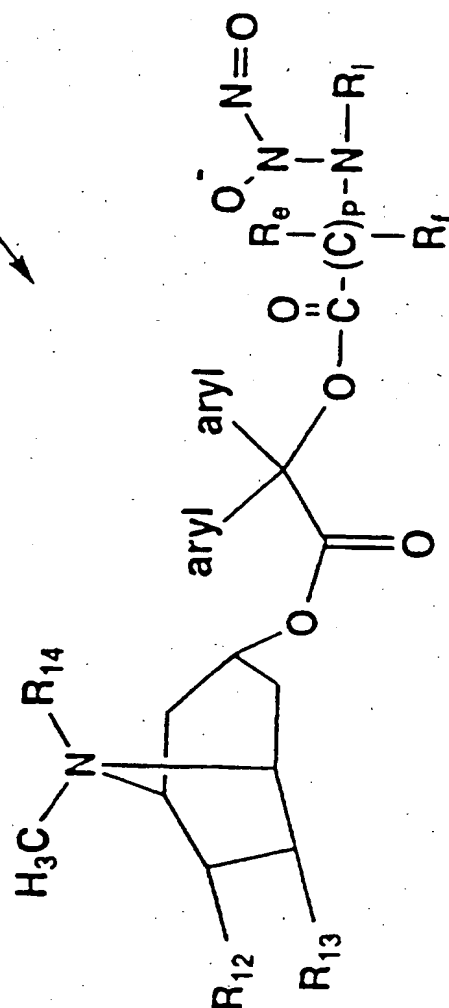
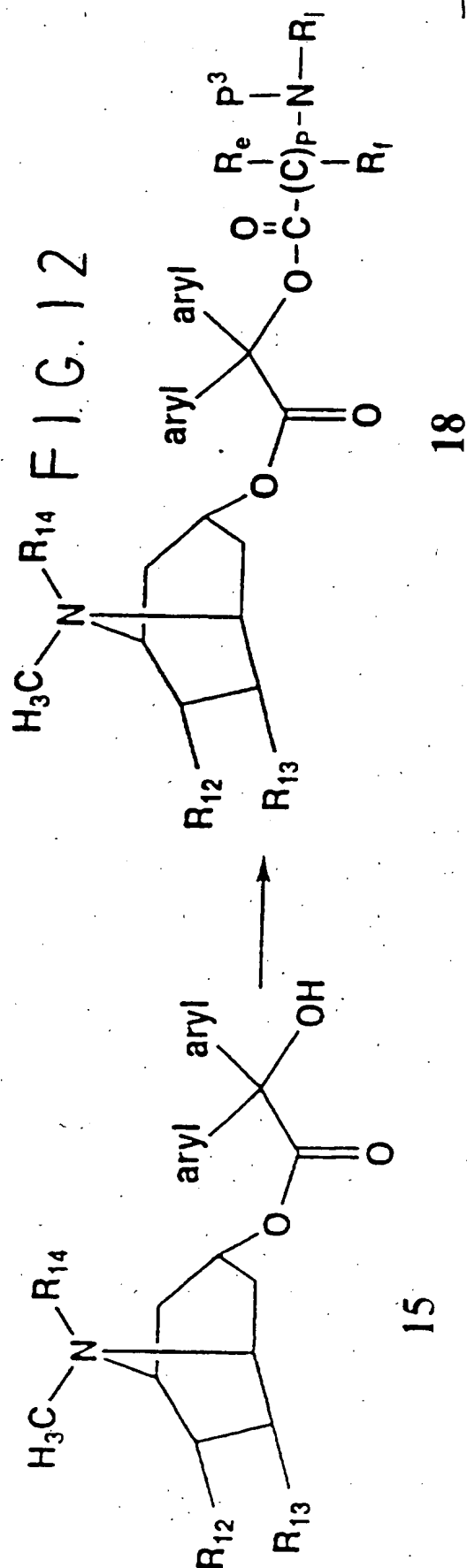
FIG. 10



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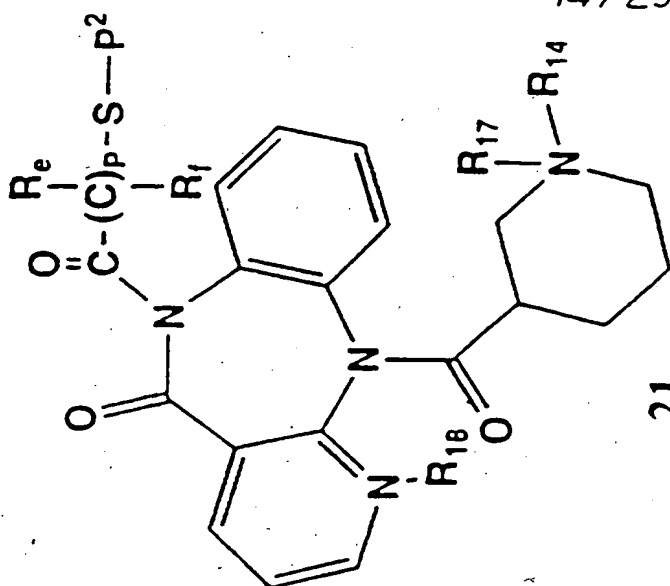
SUBSTITUTE SHEET (RULE 26)

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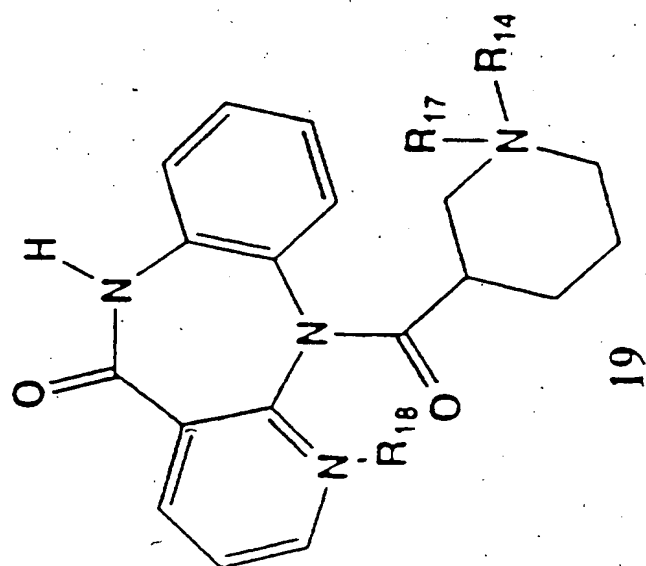
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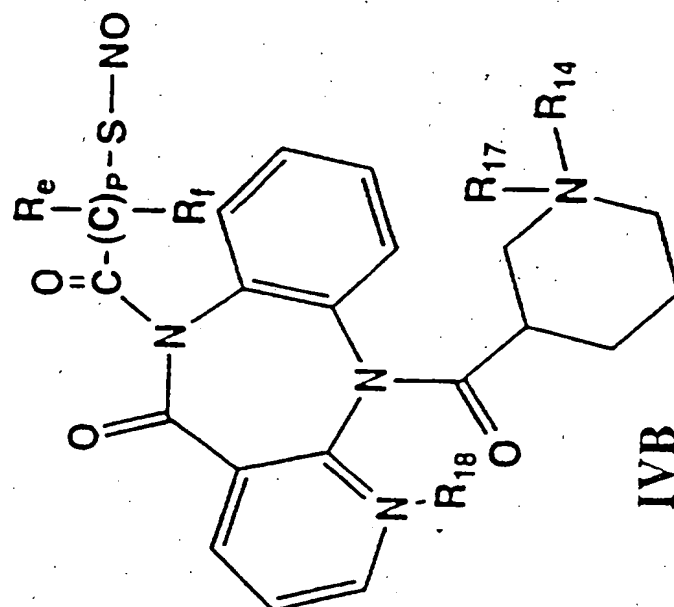


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FIG. 14

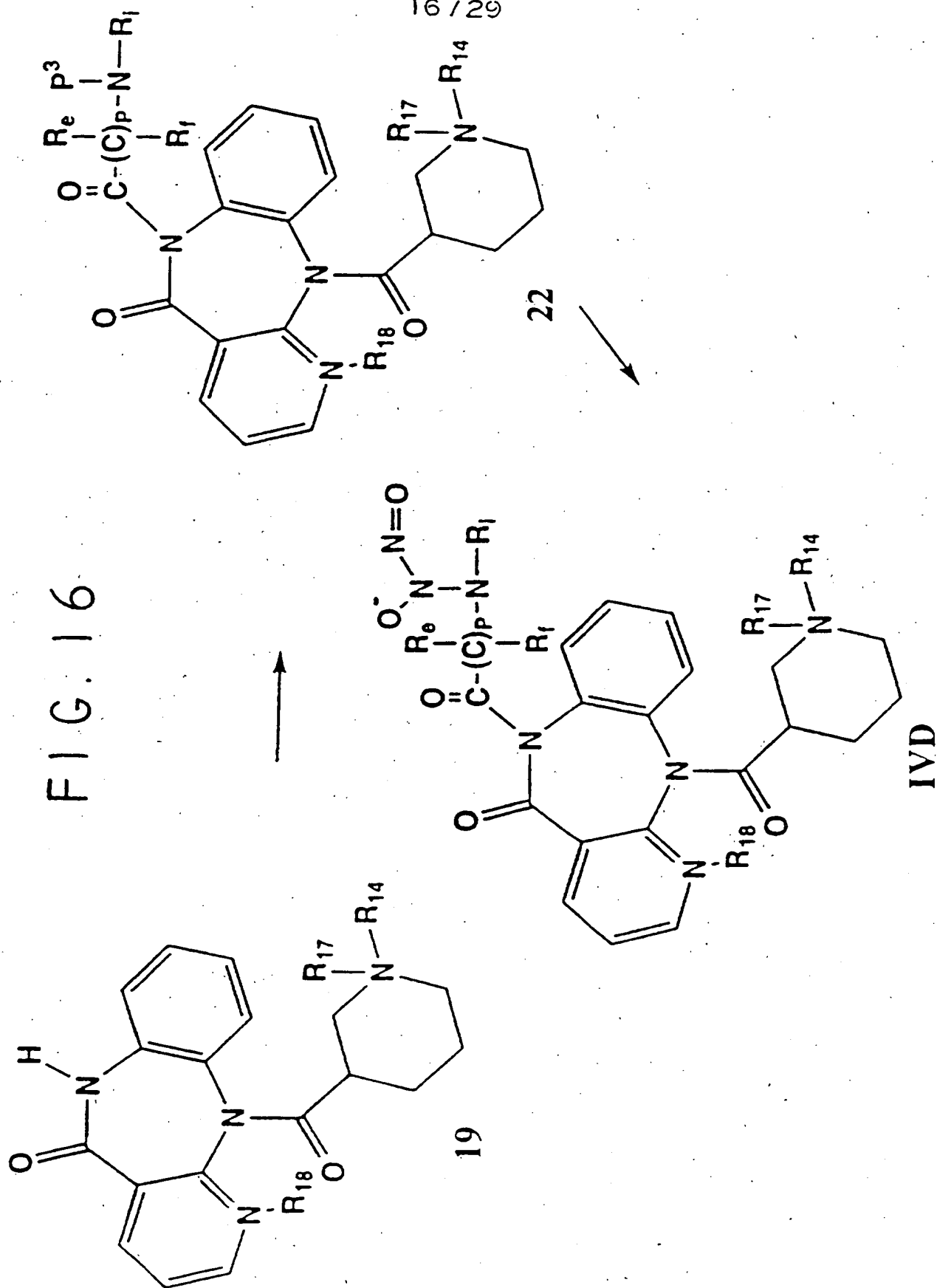


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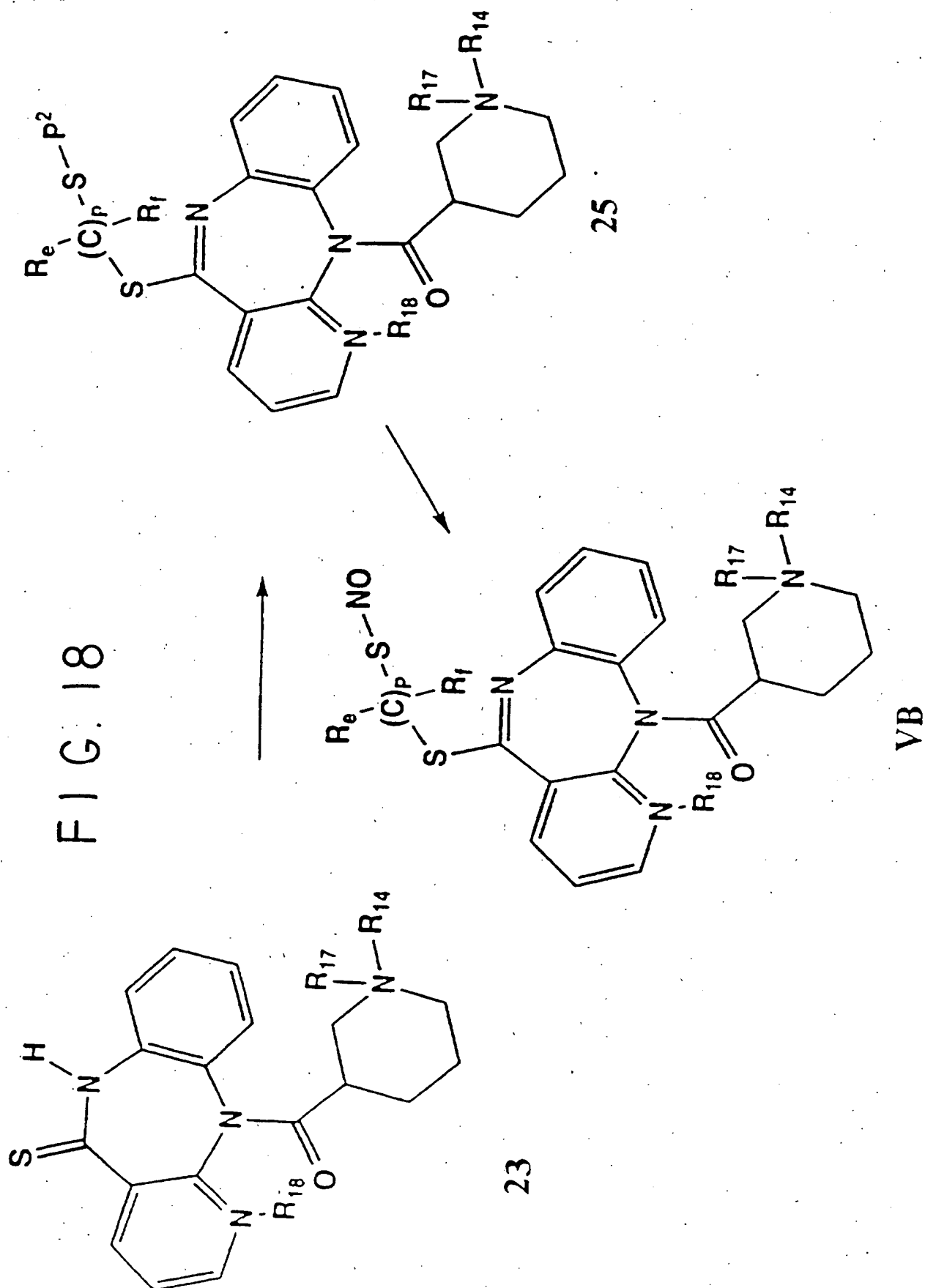


IVB

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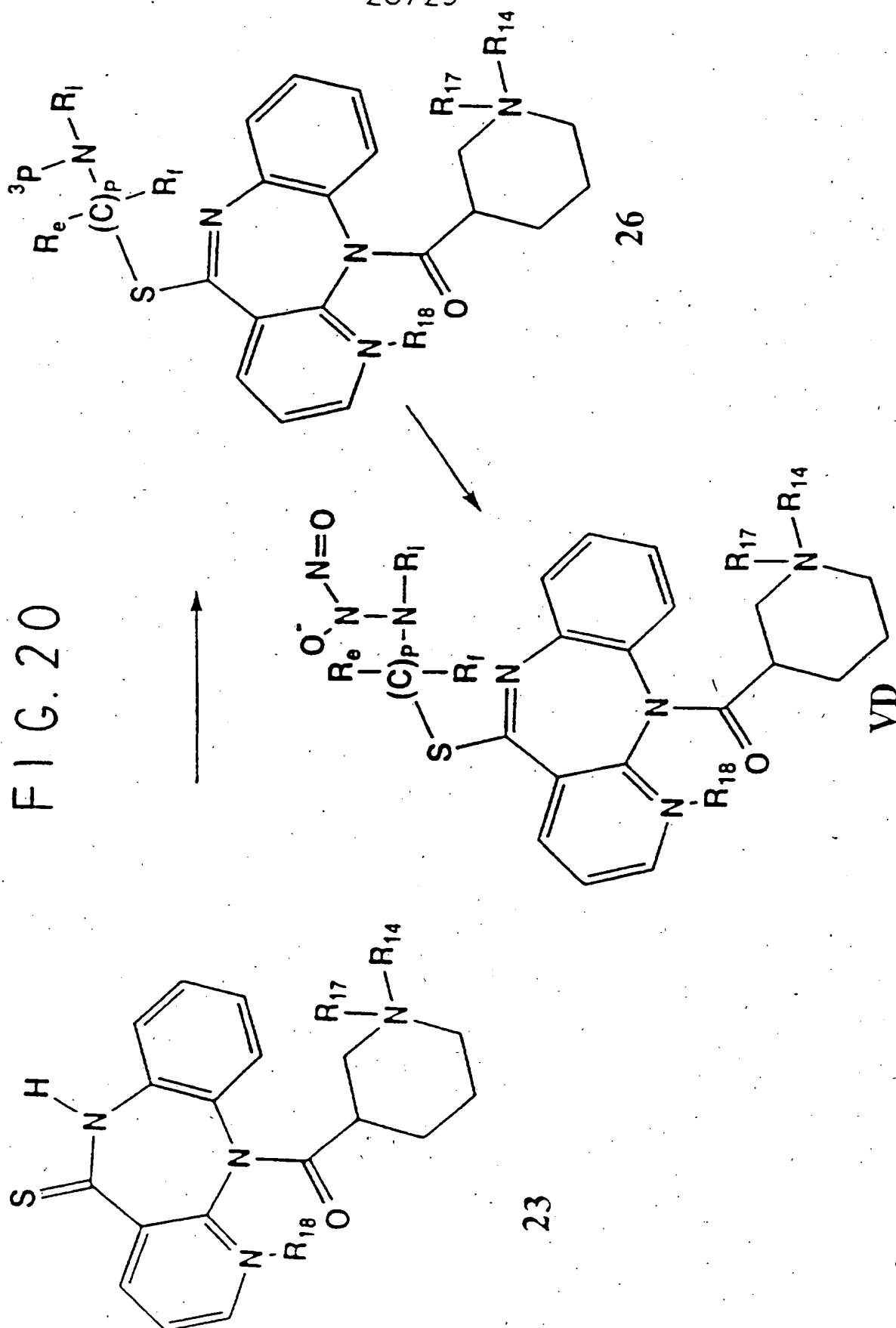


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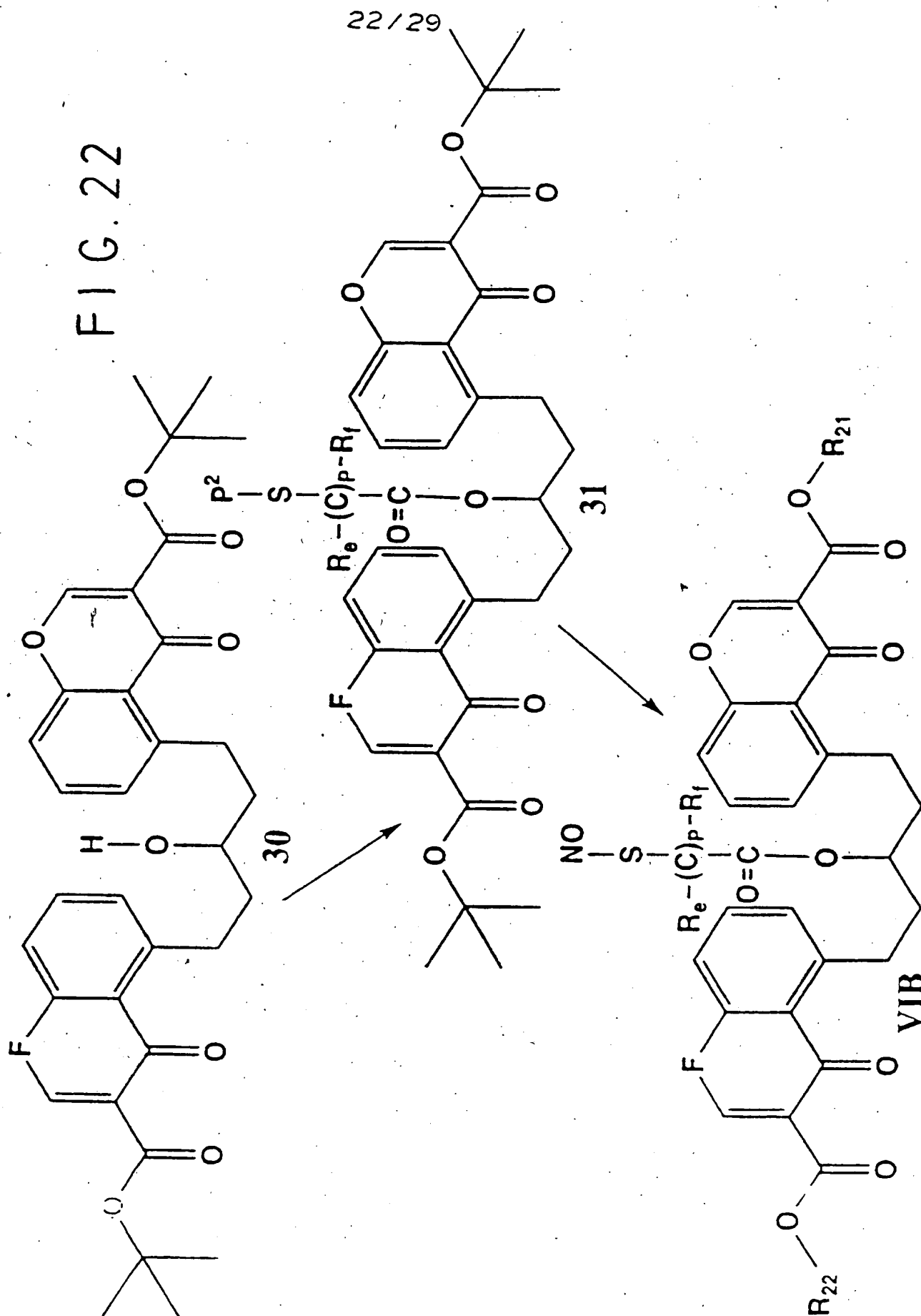
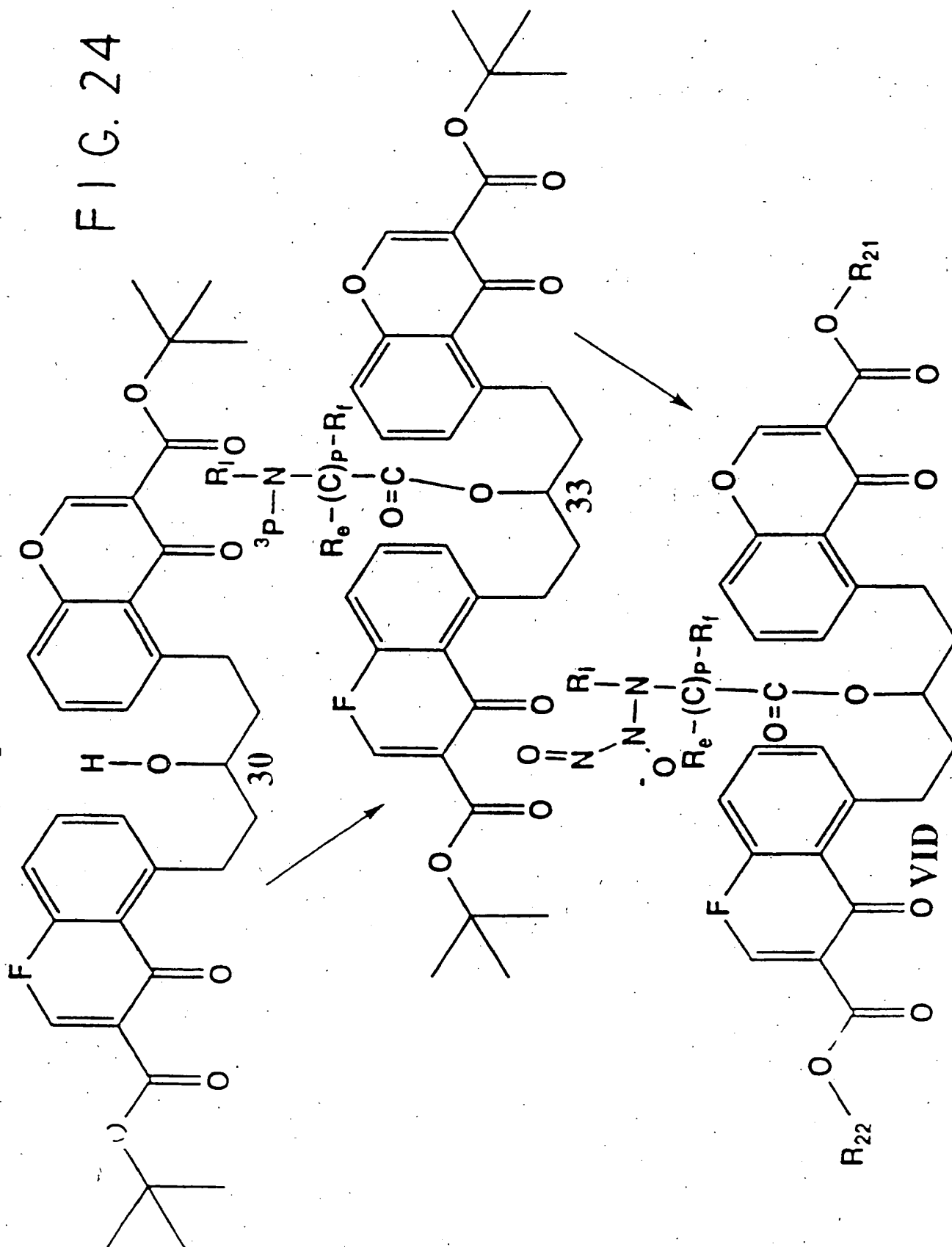
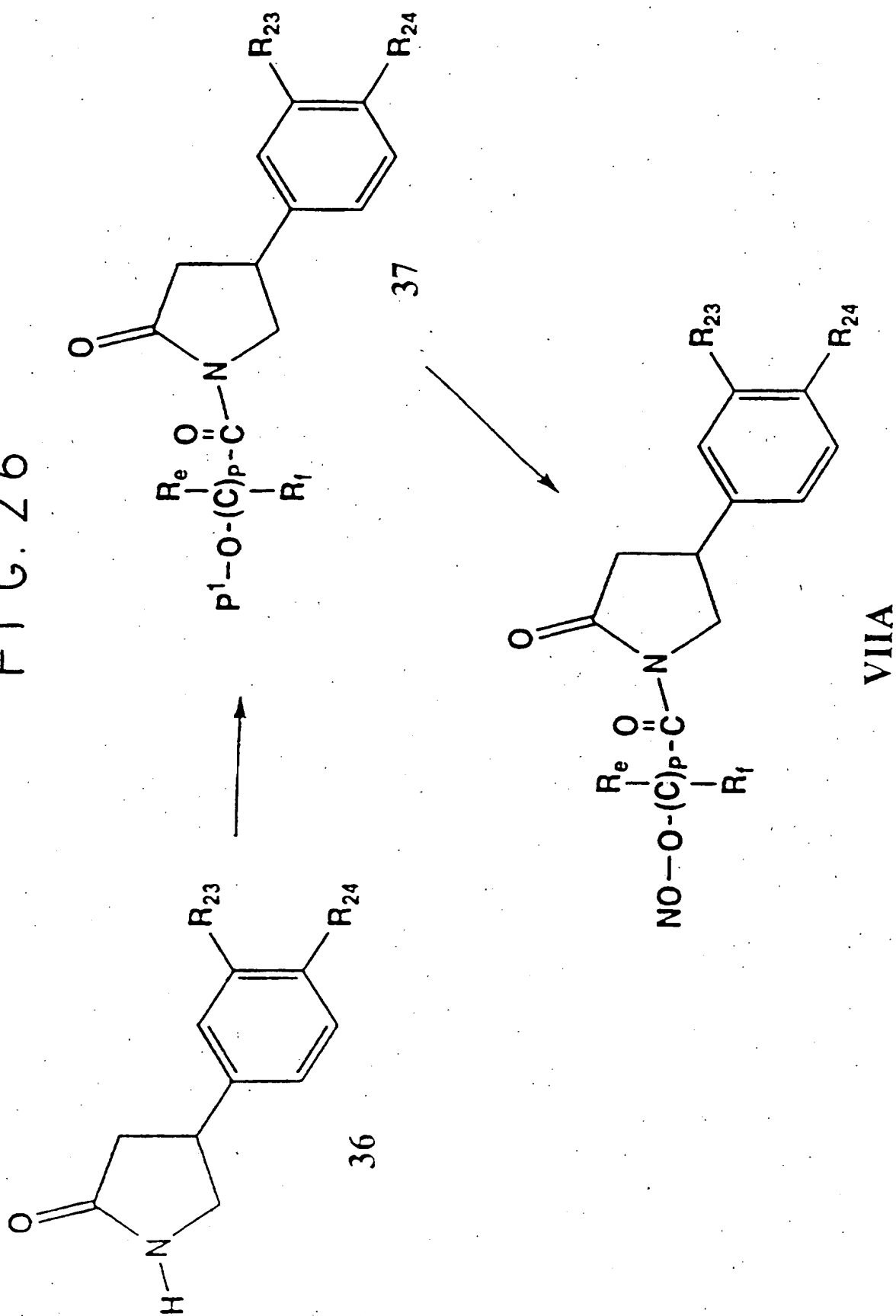


FIG. 24



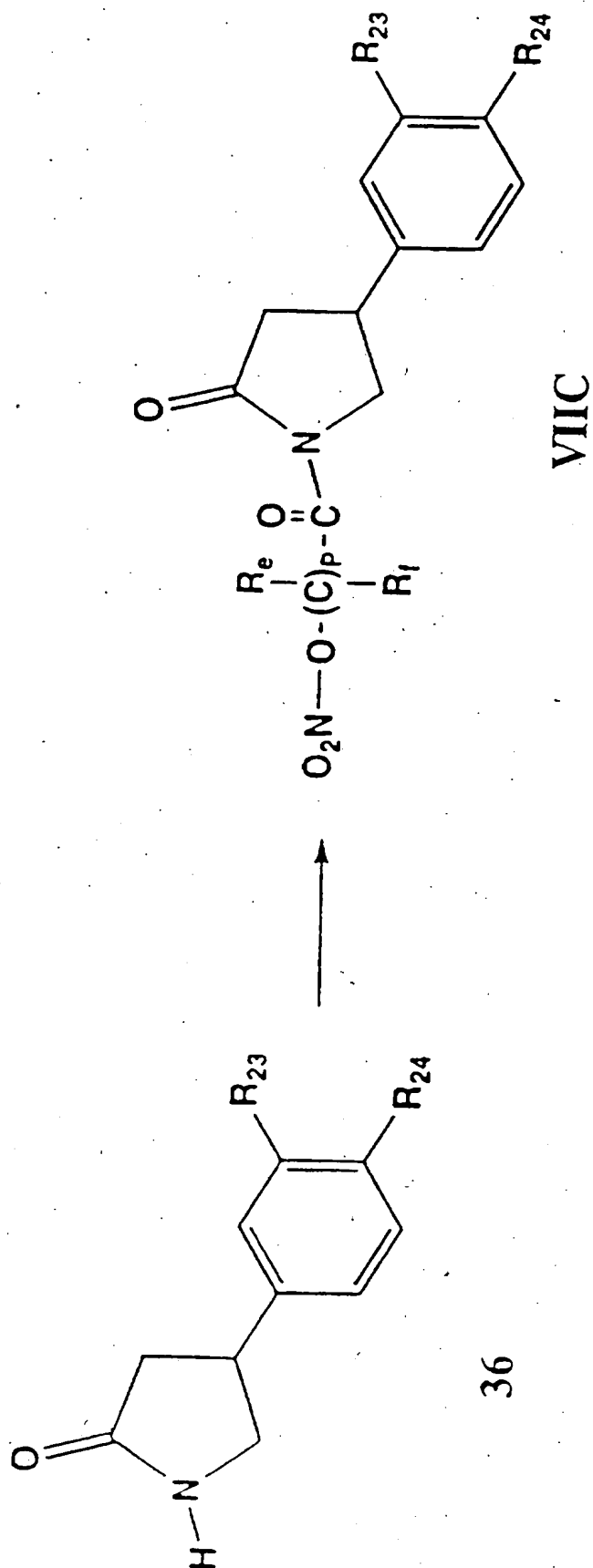
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FIG. 26



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FIG. 28



SUBSTITUTE SHEET (RULE 26)

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/04319

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
CAS ONLINE (STN DATABASES) File Registry, File Beilstein, File Marpat**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BUDAVARI et al. The Merck Index. Rahway, N.J.: Merck & Co., Inc. 1989, pages 648-650, see entire document.	1-16 (in part)

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

Special categories of cited documents:		
"A"	document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E"	earlier document published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	
"P"	document published prior to the international filing date but later than the priority date claimed	"A" document member of the same patent family

Date of the actual completion of the international search

22 JUNE 1997

Date of mailing of the international search report

04 AUG 1997

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

ALAN L. ROTMAN

Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)\*

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/04319

## A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6):

C07D 211/18, 211/32, 211/68, 213/40, 223/10, 243/00, 279/12, 311/74, 401/06; C07J 7/00

## A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

540/485, 492; 544/58.1, 238, 265; 546/232, 235, 285; 548/465, 467; 549/402; 552/567, 581; 556/572, 573, 575, 575; 564/305

## B. FIELDS SEARCHED:

540/485, 492; 544/58.1, 238, 265; 546/232, 235, 285; 548/465, 467; 549/402; 552/567, 581; 556/572, 573, 575, 575; 564/305

## BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

**GROUP I:** Claims 1-16 (in-part), drawn to steroidal compounds, compositions and methods of use wherein the term "A" in the depicted formula I represents -CH=CH- or -CH<sub>2</sub>-CH<sub>2</sub>-; (R1) is selected from -C(=O)CH<sub>2</sub>-B-D wherein "B" is oxygen or sulfur; "D" is selected from NO or NO<sub>2</sub>; (Rc and Rf) each occurrence is selected from H, Lower alkyl, cycloalkyl, and aryl; (R2) and (R3) represent H or lower alkyl; (R4) and (R5) represent hydrogen or halogen. Class 556, Subclasses 572, 573, 575 and 577.

**GROUP II:** Claims 1-16 (in-part) and Group I, except that the term (R1) represents the grouping C(Rd)-O-C(O)-Y-[C(re)(Rf)p-T-Q wherein said individual terms are as defined in claim I, formula I. Class 552, Subclasses 567 and 581.

**GROUP III:** Claims 1-16 (in-part), corresponding to the formula II. Class 546, Subclass 285; Class 564, Subclass 305.

**GROUP IV:** Claims 1-16 (in-part), corresponding to the formula III, which is an imidazo[4,5-d]pyrimidine-2,4-dione derivative. Class 544, Subclass 265.

**GROUP V:** Claims 1-16 (in-part), corresponding to the formula III(2), which is a piperidine. Class 546, Subclasses 232 and 235.

**GROUP VI:** Claims 1-16 (in-part), corresponding to the formulas III(1), (2), (3), which is an 1-aza-bicyclo[2.2.1]heptane ester. Class 548, Subclasses 465 and 467.

**GROUP VII:** Claims 1-16 (in-part), corresponding to the formulas IV and V, which correspond to Pyrido[4,3-b][1,5]benzodiazepine derivatives. Class 540, Subclasses 485 and 492.

**GROUP VIII:** Claims 1-16 (in-part), corresponding to the formula VI and derivatives thereof which correspond to bis-[(4-oxo-benzopyran)-3-carboxylates]. Class 546, Subclass 268.1; Class 548, Subclasses 125 and 518; Class 549, Subclass 402.

**GROUP IX:** Claims 1-16 (in-part), corresponding to the formula VII which corresponds to a phenyl moiety substituted with a member selected from 2-pyrrolidone, 2-imino-4-oxo-tetrahydro-1,3-thiazine, 3-oxo-pyridazine. Class 544, Subclasses 58.1 and 238; Class 548, Subclass 518.

and it considers that the International Application does not comply with the requirements of unity of invention (Rules 13.1, 12.2 and 13.3) for the reason indicated below:

Lack of unity of invention has been found to exist because each Group represents diverse core structures which are not art recognized equivalents and clearly represent independent and distinct inventions.